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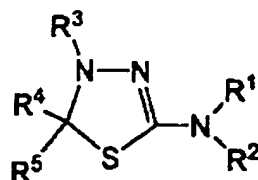
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(54) **THIADIAZOLINE DERIVATIVE**

(57)



(I)

(wherein R¹ and R⁴ are the same or different and each represents a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, or the like; R⁵ represents a substituted or unsubstituted heterocyclic group, substituted or unsubstituted aryl, or the like; R² represents -C(-W)R⁶ or the like; R³ represents a hydrogen atom, -C(=W^A)R^{8A}, or the like)

Antitumor agents which comprises a thiadiazoline derivative represented by the aforementioned general formula (I) or a pharmacologically acceptable salt thereof as an active ingredient are provided.

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Description**Technical Field**

5 [0001] The present invention relates to an antitumor agent comprising a thiadiazoline derivative or a pharmacologically acceptable salt thereof as an active ingredient, and a thiadiazoline derivative or a pharmacologically acceptable salt thereof which is useful for therapeutic treatment of a tumor.

Background Art

10 [0002] In chemotherapies of cancers, a variety of anticancer agents including antimitotic agents such as taxane and vinca alkaloid, topoisomerase inhibitors, alkylating agents and the like have been used. These agents have side effects such as bone marrow toxicity and neuropathy, a problem of drug resistance and the like. Therefore, novel anticancer agents which have improvement in the above problems have so far been desired.

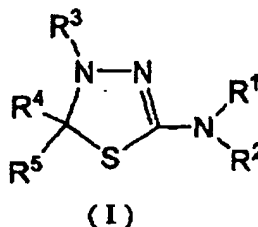
15 [0003] It is known that thiadiazoline derivatives have inhibitory activity against transcription factor STAT6 activation, antagonistic action of integrin, and the control of insect or acarid pests (Japanese Published Unexamined Patent Application No. 2000-229959, WO01/56994, US6235762). In addition, it is known that the derivatives have antibacterial activity, ACE inhibitory activity and the like [J. Bangladesh Chem. Soc., Vol. 5, p. 127 (1992), WO93/22311, Japanese Published Unexamined Patent Application No. 62-53976 (1987)].

Disclosure of the Invention

20 [0004] An object of the present invention is to provide a thiadiazoline derivative or a pharmacologically acceptable salt thereof which is useful for therapeutic treatment of a human malignant tumor, for example, breast cancer, gastric cancer, ovarian cancer, colon cancer, lung cancer, brain tumor, laryngeal cancer, hematological cancer, urinary or genital tumor including bladder cancer and prostatic cancer, renal cancer, skin carcinoma, hepatic carcinoma, pancreatic cancer, a uterine cancer, or the like. Another object of the present invention is to provide an antitumor agent comprising a thiadiazoline derivative or a pharmacologically acceptable salt thereof as an active ingredient.

30 [0005] The present invention relates to the following (1) to (43).

(1) An antitumor agent which comprises a thiadiazoline derivative represented by the general formula (I) or a pharmacologically acceptable salt thereof as an active ingredient



45 <wherein

R¹ and R⁴ are the same or different and each represents

a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocyclic group, or substituted or unsubstituted aryl;

R² represents

50 a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted cycloalkyl,

-C(=W)R⁶ [wherein

W represents

an oxygen atom or a sulfur atom

55 R⁶ represents

a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted cycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heterocyclic group,

-NR⁷R⁸ (wherein
 R⁷ and R⁸ are the same or different and each represents
 a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower
 5 alkenyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or a substituted or unsubstituted
 heterocyclic group, or
 R⁷ and R⁸ are combined together with the adjacent nitrogen atom to form a substituted or unsub-
 stituted heterocyclic group);
 -OR⁹ (wherein
 R⁹ represents
 10 substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted
 or unsubstituted cycloalkyl, or substituted or unsubstituted aryl) or
 -SR¹⁰ (wherein
 R¹⁰ represents
 substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, or substi-
 15 tuted or unsubstituted aryl)]
 -NR¹¹R¹² {wherein
 R¹¹ and R¹² are the same or different and each represents
 a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl,
 substituted or unsubstituted cycloalkyl, or
 20 -C(=O)R¹³ {wherein
 R¹³ represents
 substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted
 or unsubstituted aryl, a substituted or unsubstituted heterocyclic group,
 -NR^{7A}R^{8A} (wherein R^{7A} and R^{8A} have the same meanings as those of the aforementioned R⁷
 25 and R⁸, respectively), or
 -OR^{9A} (wherein R^{9A} has the same meaning as that of the aforementioned R⁹)} or
 -SO₂R¹⁴ (wherein
 R¹⁴ represents
 substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or un-
 30 substituted aryl, or a substituted or unsubstituted heterocyclic group), or
 R¹ and R² are combined together with the adjacent nitrogen atom to form a substituted or unsubstituted heterocyclic
 group,
 R⁵ represents
 substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted
 35 lower alkenyl, substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocyclic group, or substi-
 tuted or unsubstituted aryl, or
 R⁴ and R⁵ are combined together to represent
 -(CR²⁸R²⁹)_{m1}-Q-(CR^{28A}R^{28A})_{m2}- {wherein
 Q represents
 40 a single bond, substituted or unsubstituted phenylene, or cycloalkylene,
 m1 and m2 are the same or different and each represents
 an integer of from 0 to 4, with the proviso that m1 and m2 are not 0 at the same time,
 R²⁸, R²⁹, R^{28A} and R^{28A} are the same or different and each represents
 a hydrogen atom, substituted or unsubstituted lower alkyl,
 45 -OR³⁰ {wherein
 R³⁰ represents
 a hydrogen atom,
 substituted or unsubstituted lower alkyl,
 substituted or unsubstituted lower alkenyl,
 50 -CONR³¹R³² (wherein
 R³¹ and R³² are the same or different and each represents
 a hydrogen atom, substituted or unsubstituted lower alkyl, a substituted or unsubstituted
 heterocyclic group, or substituted or unsubstituted aryl),
 -SO₂NR³³R³⁴ (wherein
 55 R³³ and R³⁴ are the same or different and each represents
 a hydrogen atom, substituted or unsubstituted lower alkyl, a substituted or unsubstituted
 heterocyclic group, or substituted or unsubstituted aryl), or
 -COR³⁵ (wherein

R³⁵ represents

a hydrogen atom, substituted or unsubstituted lower alkyl, a substituted or unsubstituted heterocyclic group, or substituted or unsubstituted aryl),

-NR³⁶R³⁷ (wherein

R³⁶ and R³⁷ are the same or different and each represents

a hydrogen atom,

substituted or unsubstituted lower alkyl,

-COR³⁸ (wherein

R³⁸ represents

a hydrogen atom, substituted or unsubstituted lower alkyl, a substituted or unsubstituted heterocyclic group, substituted or unsubstituted aryl, substituted or unsubstituted lower alkoxy, substituted or unsubstituted aryloxy, amino, substituted or unsubstituted lower alkylamino, substituted or unsubstituted di(lower alkyl)amino, or substituted or unsubstituted arylamino), or

-SO₂R³⁹ (wherein

R³⁹ represents

substituted or unsubstituted lower alkyl, a substituted or unsubstituted heterocyclic group, or substituted or unsubstituted aryl), or

-CO₂R⁴⁰ (wherein

R⁴⁰ represents

a hydrogen atom, substituted or unsubstituted lower alkyl, or substituted or unsubstituted aryl), and

when m₁ or m₂ is an integer of 2 or more, each R²⁸, R²⁹, R^{28A} and R^{29A} may be the same or different, respectively, and any two of R²⁸, R²⁹, R^{28A} and R^{29A} which are bound to the adjacent two carbon atoms may be combined to form a bond, and R³ represents

a hydrogen atom or

-C(=W^A)R^{6A} (wherein W^A and R^{6A} have the same meanings as those of the aforementioned W and R⁶, respectively).

(2) The antitumor agent according to the aforementioned (1), wherein R⁴ is substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocyclic group, or substituted or unsubstituted aryl, and R⁵ is substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocyclic group, or substituted or unsubstituted aryl, or R⁴ and R⁵ are combined to represent -(CR²⁸R²⁹)_{m1}-Q-(CR^{28A}R^{29A})_{m2}.

(3) The antitumor agent according to the aforementioned (1), wherein R⁵ is substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted cycloalkyl.

(4) The antitumor agent according to the aforementioned (1) or (2), wherein R⁵ is substituted or unsubstituted aryl, or a substituted or unsubstituted heterocyclic group.

(5) The antitumor agent according to the aforementioned (1) or (2), wherein R⁵ is substituted or unsubstituted phenyl, or substituted or unsubstituted thienyl.

(6) The antitumor agent according to any one of the aforementioned (1) to (5), wherein R⁴ is substituted or unsubstituted lower alkyl.

(7) The antitumor agent according to the aforementioned (1), wherein R⁴ and R⁵ are combined to represent -(CR²⁸R²⁹)_{m1}-Q-(CR^{28A}R^{29A})_{m2}.

(8) The antitumor agent according to the aforementioned (1), wherein R⁴ and R⁵ are combined to represent -(CH₂)_{m1}-Q-(CH₂)_{m2}.

(9) The antitumor agent according to the aforementioned (7) or (8), wherein Q is substituted or unsubstituted phenylene.

(10) The antitumor agent according to any one of the aforementioned (1) to (9), wherein R¹ is a hydrogen atom, or substituted or unsubstituted lower alkyl.

(11) The antitumor agent according to any one of the aforementioned (1) to (9), wherein R¹ is a hydrogen atom.

(12) The antitumor agent according to any one of the aforementioned (1) to (11), wherein R² is -C(=W)R⁶.

(13) The antitumor agent according to the aforementioned (12), wherein R⁶ is substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted cycloalkyl.

(14) The antitumor agent according to the aforementioned (12) or (13), wherein W is an oxygen atom.

(15) The antitumor agent according to any one of the aforementioned (1) to (9), wherein R¹ and R² are combined to form a substituted or unsubstituted heterocyclic group together with the adjacent nitrogen atom.

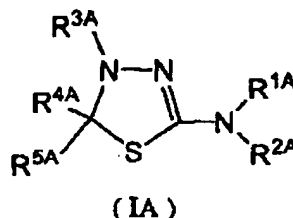
(16) The antitumor agent according to any one of the aforementioned (1) to (15), wherein R³ is -C(=W^A)R^{6A}.

(17) The antitumor agent according to the aforementioned (16), wherein R^{8A} is substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted cycloalkyl.

(18) The antitumor agent according to the aforementioned (16), wherein R^{8A} is lower alkyl.

(19) The antitumor agent according to any one of the aforementioned (16) to (18), wherein W^A is an oxygen atom.

(20) A thiadiazoline derivative represented by the general formula (IA) or a pharmacologically acceptable salt thereof:



{wherein R^{1A} , R^{2A} , R^{3A} , R^{4A} and R^{5A} have the same meanings as those of the aforementioned R^1 , R^2 , R^3 , R^4 and R^5 , respectively, with the proviso that when R^{2A} and R^{3A} are the same to be $-\text{CONHR}^{8B}$ (wherein R^{8B} represents a substituted or unsubstituted lower alkyl, or substituted or unsubstituted aryl), and

(i) R^{4A} is a hydrogen atom, or

(ii) one of R^{4A} and R^{5A} is substituted or unsubstituted lower alkyl, then the other of R^{4A} and R^{5A} only represents substituted or unsubstituted cycloalkyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted lower alkynyl

[provided that

(a) when R^{1A} , R^{2A} and R^{3A} are hydrogen atoms, and one of R^{4A} and R^{5A} is methyl,

the other of R^{4A} and R^{5A} is not any of phenyl, 4-nitrophenyl, 4-aminophenyl, 4-bromophenyl, 3-nitrophenyl and 4-methoxy-3-nitrophenyl,

(b) when R^{1A} and R^{2A} are hydrogen atoms, R^{3A} is acetyl,

(i) and one of R^{4A} and R^{5A} is methyl,

the other of R^{4A} and R^{5A} is not any of methyl, ethyl, phenyl, 4-methoxyphenyl, 2-naphthylsulfonylmethyl, 4-bromophenylsulfonylmethyl and 4-chlorophenylsulfonylmethyl, and

(ii) and R^{4A} is a hydrogen atom,

R^{5A} is not any of phenyl, 4-nitrophenyl, 4-chlorophenyl, 4-methoxyphenyl, 4-dimethylaminophenyl and pyridyl,

(c) when R^{1A} is a hydrogen atom, R^{2A} and R^{3A} are acetyl,

(i) and one of R^{4A} and R^{5A} is methyl,

the other of R^{4A} and R^{5A} is not any of methyl, ethyl, propyl, butyl, hexyl, heptyl, phenyl, benzyl, acetylmethyl, tert-butoxycarbonylmethyl, ethoxycarbonylmethyl, 4-bromophenylsulfonylmethyl, 4-bromophenylsulfonylethyl, 4-chlorophenylsulfonylmethyl, 3,4-dichlorophenylsulfonylmethyl, 3,4-dichlorophenylsulfonylethyl, 3,4-dimethylphenylsulfonylmethyl, phenylsulfonylmethyl, 4-methylphenylsulfonylmethyl, 4-methylphenylsulfonylethyl, 4-(acetylaminophenylsulfonylethyl, 4-bromophenylsulfonylethyl, 2-(4-methylphenylsulfonyl)-2-phenylethyl, 2-(4-methylphenylthio)-2-phenylethyl, 2-naphthylsulfonylethyl, 2-naphthylsulfonylmethyl, phenethyl, 3-benzoyloxyphenyl, 2-oxo-2H-1-benzopyran-3-yl, 2-furyl, 5-nitro-2-furyl, 5-methyl-2-furyl, 2-thienyl, 5-chloro-2-thienyl, 3-acetoxyphenyl, 3-nitrophenyl, 4-nitrophenyl, 4-fluorophenyl, 3-acetylaminophenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-ethylphenyl, 4-methylphenyl, 4-bromophenyl, 4-nonyloxyphenyl, 4-phenylphenyl, 3,4-dimethoxyphenyl, 1,3-benzodioxol-5-yl, 4-(benzimidazol-2-ylamino)phenyl, 4-(1-methylbenzimidazol-2-ylamino)phenyl, 3-pyridyl, 2-naphthyl, 2-acetylaminophenyl, 4-acetyl-1,3,4-thiadiazolin-5-yl and 4-acetylaminophenylsulfonylmethyl.

- (ii) and one of R^{4A} and R^{5A} is phenyl,
the other of R^{4A} and R^{5A} is not any of phenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 4-nitrophenyl, ethoxycarbonylmethyl, isobutyl, sec-butyl, n-butyl and acetylaminoethyl,
- (iii) and one of R^{4A} and R^{5A} is 2-acetoxyphenyl,
the other of R^{4A} and R^{5A} is not 2-phenylethenyl,
- (iv) and R^{4A} is a hydrogen atom or 4-methoxyphenyl,
 R^{5A} is not 4-methoxyphenyl,
- (v) and R^{4A} is a hydrogen atom,
 R^{5A} is not any of phenyl, 4-nitrophenyl, 4-chlorophenyl, 4-dimethylaminophenyl and pyridyl,
- (vi) and R^{4A} and R^{5A} are combined to represent
 $-(CH_2)_{m1}-Q-(CH_2)_{m2}-$ (wherein $m1$, $m2$ and Q have the same meanings as those of the aforementioned, respectively),
 $-(CH_2)_{m1}-Q-(CH_2)_{m2}-$ wherein Q is a single bond and the sum of $m1$ and $m2$ is 5, is excluded
- (vii) and one of R^{4A} and R^{5A} is 1,2,3-triacetoxypentyl,
the other of R^{4A} and R^{5A} is not 3,4-dihydro-3-oxo-2-quinoxaliny, and
- (viii) and one of R^{4A} and R^{5A} is ethyl,
the other of R^{4A} and R^{5A} is not ethyl,
- (d) when R^{1A} and R^{4A} are hydrogen atoms, and
- (i) R^{2A} and R^{3A} are the same to be propionyl or benzoyl or
- (ii) R^{2A} is propionyl and R^{3A} is acetyl,
 R^{5A} is not phenyl,
- (e) when R^{1A} and R^{3A} are hydrogen atoms,
 R^{2A} is acetyl, and
one of R^{4A} and R^{5A} is methyl,
the other of R^{4A} and R^{5A} is not either of phenyl and 3,4-dichlorophenylsulfonylethyl,
- (f) when R^{1A} is phenyl, R^{2A} and R^{3A} are acetyl,
- (i) and one of R^{4A} and R^{5A} is methyl,
the other of R^{4A} and R^{5A} is not either of 4-acetoxy-6-methyl-2-oxo-2H-pyran-3-yl and 2-oxo-2H-1-benzopyran-3-yl, and
- (ii) and R^{4A} is phenyl,
 R^{5A} is not phenyl,
- (g) when R^{1A} is methyl, R^{2A} and R^{3A} are acetyl,
- (i) and R^{4A} is a hydrogen atom,
 R^{5A} is not phenyl,
- (ii) and one of R^{4A} and R^{5A} is methyl,
the other of R^{4A} and R^{5A} is not either of ethoxycarbonylethyl and ethoxycarbonylpropyl,
- (h) when R^{1A} , R^{2A} and R^{4A} are methyl, and
 R^{5A} is pyridyl,
 R^{3A} is not $-COR^C$ (wherein R^C represents methyl, chloromethyl, methoxy, ethoxycarbonylmethyl or ethoxycarbonylethyl),
- (i) when one of R^{1A} and R^{2A} is a hydrogen atom,
the other of R^{1A} and R^{2A} is ethyl, and
 R^{3A} is a hydrogen atom or acetyl,
 R^{4A} and R^{5A} are not methyl at the same time,
- (k) when R^{1A} is 4-chlorophenyl,
 R^{2A} is a hydrogen atom, and
one of R^{4A} and R^{5A} is methyl,
the other of R^{4A} and R^{5A} is not (1-methylbenzimidazol-2-ylamino)phenyl, and
 R^{3A} is not acetyl,
- (m) when R^{1A} is phenyl, 4-chlorophenyl, 4-methylphenyl or 4-methoxyphenyl,
 R^{2A} is a hydrogen atom, and

R^{4A} and R^{5A} are methyl,

R^{3A} is not any of acetyl, 4-chlorophenoxyacetyl, 2-chlorophenoxyacetyl, 3-methylphenoxyacetyl and phenylaminocarbonyl,

(n) when R^{2A} and R^{3A} are acetyl,

one of R^{4A} and R^{5A} is methyl,

(i) and the other of R^{4A} and R^{5A} is 1H-benzotriazol-1-ylmethyl,

R^{1A} is not any of cyclohexyl, benzyl, phenyl, 2-methylphenyl and 4-methoxyphenyl,

(ii) and the other of R^{4A} and R^{5A} is 2-methylbenzimidazol-1-ylmethyl or 2-ethylbenzimidazol-1-ylmethyl,

R^{1A} is not any of cyclohexyl, phenyl and 4-bromophenyl,

(o) when R^{1A} is a hydrogen atom,

R^{2A} is acetyl, and

R^{4A} and R^{5A} are methyl,

R^{3A} is not benzoyl,

(p) when one of R^{1A} and R^{2A} is hydrogen atom,

the other of R^{1A} and R^{2A} is methyl, and

R^{4A} and R^{5A} are both methyl or both ethyl,

R^{3A} is not any of acetyl, benzoyl, pivaloyl, 3-nitrobenzoyl, 2-fluorobenzoyl, 4-fluorobenzoyl, 2-trifluoromethylbenzoyl and 3-trifluoromethylbenzoyl, and

(q) when R^{1A} is methyl,

R^{2A} is methylaminocarbonyl, and

R^{4A} and R^{5A} are both methyl or both ethyl,

R^{3A} is not any of acetyl; benzoyl, pivaloyl, 2-fluorobenzoyl, 4-fluorobenzoyl, 2-trifluoromethylbenzoyl, 3-trifluoromethylbenzoyl and 4-trifluoromethylbenzoyl]].

(21) The thiadiazoline derivative according to the aforementioned (20), wherein R^{4A} is substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, or substituted or unsubstituted lower alkenyl, R^{5A} is substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocyclic group, or substituted or unsubstituted aryl, or R^{4A} and R^{5A} are combined to represent $-(CR^{28}R^{29})_{m1}-Q-(CR^{28}R^{29})_{m2}-$ (wherein R²⁸, R²⁹, R^{28A}, R^{29A}, m1, m2 and Q have the same meanings as those of the aforementioned, respectively), or the pharmacologically acceptable salt thereof.

(22) The antitumor agent according to the aforementioned (20), wherein R^{5A} is substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted cycloalkyl.

(23) The thiadiazoline derivative according to the aforementioned (20) or (21), wherein R^{5A} is substituted or unsubstituted aryl, or a substituted or unsubstituted heterocyclic group, or the pharmacologically acceptable salt thereof.

(24) The thiadiazoline derivative according to the aforementioned (20) or (21), wherein R^{5A} is substituted or unsubstituted phenyl or substituted or unsubstituted thienyl, or the pharmacologically acceptable salt thereof.

(25) The thiadiazoline derivative according to any one of the aforementioned (20) to (24), wherein R^{4A} is substituted or unsubstituted lower alkyl, or the pharmacologically acceptable salt thereof.

(26) The thiadiazoline derivative according to any one of the aforementioned (20) to (24), wherein R^{4A} is substituted lower alkyl, or the pharmacologically acceptable salt thereof.

(27) The thiadiazoline derivative according to the aforementioned (20), wherein R^{4A} and R^{5A} combine together to represent $-(CR^{28}R^{29})_{m1}-Q-(CR^{28}R^{29})_{m2}-$ (wherein R²⁸, R²⁹, R^{28A}, R^{29A}, m1, m2, and Q have the same meanings as those of the aforementioned, respectively), or the pharmacologically acceptable salt thereof.

(28) The thiadiazoline derivative according to the aforementioned (20), wherein R^{4A} and R^{5A} are combined to represent $-(CH_2)_{m1}-Q-(CH_2)_{m2}-$ (wherein m1, m2 and Q have the same meanings as those of the aforementioned, respectively), or the pharmacologically acceptable salt thereof.

(29) The thiadiazoline derivative according to the aforementioned (27) or (28), wherein Q is substituted or unsubstituted phenylene, or the pharmacologically acceptable salt thereof.

(30) The thiadiazoline derivative according to any one of the aforementioned (20) to (29), wherein R^{1A} is a hydrogen atom, or substituted or unsubstituted lower alkyl, or the pharmacologically acceptable salt thereof.

(31) The thiadiazoline derivative according to any one of the aforementioned (20) to (29), wherein R^{1A} is a hydrogen atom, or the pharmacologically acceptable salt thereof.

(32) The thiadiazoline derivative according to any one of the aforementioned (20) to (31), wherein R^{2A} is $-C(=W)R^6$ (wherein W and R⁶ have the same meanings as those of the aforementioned, respectively), or the pharmacologically acceptable salt thereof.

(33) The thiadiazoline derivative according to the aforementioned (32), wherein R^6 is substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted cycloalkyl, or the pharmacologically acceptable salt thereof.

(34) The thiadiazoline derivative according to the aforementioned (32) or (33), wherein W is an oxygen atom, or the pharmacologically acceptable salt thereof.

(35) The thiadiazoline derivative according to any one of the aforementioned (20) to (29), wherein R^{1A} and R^{2A} are combined together with the adjacent nitrogen atom to form a substituted or unsubstituted heterocyclic group, or the pharmacologically acceptable salt thereof.

(36) The thiadiazoline derivative according to any one of the aforementioned (20) to (35), wherein R^{3A} is $-C(=W^A)$ R^{6A} (wherein W^A and R^{6A} have the same meanings as those of the aforementioned, respectively), or the pharmacologically acceptable salt thereof.

(37) The thiadiazoline derivative according to the aforementioned (36), wherein R^{6A} is substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted cycloalkyl, or the pharmacologically acceptable salt thereof.

(38) The thiadiazoline derivative according to the aforementioned (36), wherein R^{6A} is lower alkyl, or the pharmacologically acceptable salt thereof.

(39) The thiadiazoline derivative according to any one of the aforementioned (36) to (38), wherein W^A is an oxygen atom, or the pharmacologically acceptable salt thereof.

(40) A pharmaceutical composition which comprises the thiadiazoline derivative according to any one of the aforementioned (20) to (39) or a pharmacologically acceptable salt thereof as an active ingredient.

(41) An antitumor agent which comprises the thiadiazoline derivative according to any one of the aforementioned (20) to (39) or a pharmacologically acceptable salt thereof as an active ingredient.

(42) Use of the thiadiazoline derivative according to any one of the aforementioned (20) to (39) or a pharmacologically acceptable salt thereof for the manufacture of an antitumor agent.

(43) A method for the treatment of malignant tumor comprising administering an effective amount of the thiadiazoline derivative according to any one of the aforementioned (20) to (39) or a pharmacologically acceptable salt thereof.

[0006] Hereinafter, compounds represented by the general formulae (I) and (IA) are referred to as Compound (I) and Compound (IA), respectively. The compounds having the other formula numbers are referred to in the same manner.

[0007] In the definition of each group of Compound (I) and Compound (IA),

(i) examples of the lower alkyl moiety in the lower alkyl, the lower alkoxy, the lower alkylamino and the di(lower alkyl)amino include straight or branched chain alkyl having 1 to 10 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl and the like.

The two lower alkyl moieties in the di(lower alkyl)amino may be the same or different.

(ii) Examples of the cycloalkyl include cycloalkyl having 3 to 8 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like.

Examples of the cycloalkylene include cycloalkylene having 3 to 8 carbon atoms, for example, cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene, cycloheptylene, cyclooctylene and the like.

(iii) Examples of the lower alkenyl include straight or branched chain alkenyl having 2 to 8 carbon atoms, for example, vinyl, allyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl and the like.

(iv) Examples of the lower alkynyl include straight or branched chain alkynyl having 2 to 8 carbon atoms, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl and the like.

(v) Examples of the aryl moiety in the aryl, the aryloxy and the arylamino include phenyl, naphthyl and the like.

(vi) Examples of the heterocyclic group include an aliphatic heterocyclic group, an aromatic heterocyclic group and the like. Examples of the aliphatic heterocyclic group include a 5- or 6-membered monocyclic aliphatic heterocyclic group containing at least one atom selected from a nitrogen atom, an oxygen atom and a sulfur atom, and a bicyclic or tricyclic condensed aliphatic heterocyclic group comprising 3- to 8-membered rings and containing at least one atom selected from a nitrogen atom, an oxygen atom and a sulfur atom, and the like, for example, pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, piperidino, morpholino, oxazolinyl, dioxolanyl, tetrahydropyranyl and the like. Examples of the aromatic heterocyclic group include a 5- or 6-membered monocyclic aromatic heterocyclic group containing at least one atom selected from a nitrogen atom, an oxygen atom and a sulfur atom, and a bicyclic or tricyclic condensed aromatic heterocyclic group comprising 3- to 8-membered rings and containing at least one atom selected from a nitrogen atom, an oxygen atom and a sulfur atom, and the like, for example, furyl, thienyl, benzothienyl, pyrrolyl, pyridyl, pyrazinyl, imidazolyl, pyrazolyl, triazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxazolyl, oxadiazolyl, pyrimidinyl, indolyl, isoindolyl, benzothiazolyl, benzimida-

zoyl, benzotriazolyl, quinolyl, isoquinolyl, quinazoliny, pyranyl and the like.

(vii) Examples of the heterocyclic group formed together with the adjacent nitrogen atom include an aliphatic heterocyclic group containing at least one nitrogen atom, and the like. Said aliphatic heterocyclic group containing at least one nitrogen atom may contain an oxygen atom, a sulfur atom or another nitrogen atom, and examples thereof include, for example, pyrrolidinyl, morpholino, thiomorpholino, pyrazolidinyl, piperidino, piperazinyl, homopiperazinyl, aziridinyl, azetidiny, azolidinyl, perhydroazepinyl, perhydroazocinyl, succinimidyl, pyrrolidonyl, glutarimidyl, piperidonyl and the like.

(viii) The substituents in the substituted lower alkyl, the substituted lower alkoxy, the substituted lower alkenyl, the substituted lower alkynyl, the substituted cycloalkyl, the substituted lower alkylamino, and the substituted di(lower alkyl)amino may be the same or different and include for example, 1 to 3 substituent(s), such as halogen, oxo, hydroxy, nitro, azide, cycloalkyl, aryl, a heterocyclic group, substituted aryl (the substituent in said substituted aryl has the same meaning as that of the after-mentioned substituent (xii) in the substituted aryl), a substituted heterocyclic group (the substituent in said substituted heterocyclic group has the same meaning as that of the after-mentioned substituent (xiii) in the substituted heterocyclic group), -CONR¹⁵R¹⁶ <wherein

R¹⁵ and R¹⁶ are the same or different and each represents

a hydrogen atom, hydroxy, cycloalkyl, lower alkyl,

lower alkenyl, aryl, a heterocyclic group,

substituted aryl (the substituent in said substituted aryl has the same meaning as that of the after-mentioned substituent (xii) in the substituted aryl),

a substituted heterocyclic group (the substituent in said substituted heterocyclic group has the same meaning as that of the after-mentioned substituent (xiii) in the substituted heterocyclic group) or

substituted lower alkyl (in said substituted lower alkyl, the substituents are the same or different and 1 to 3 substituent(s), such as

hydroxy, lower alkoxy, oxo, carboxy,

lower alkoxy carbonyl, an aryl, a heterocyclic group,

-CONR^{15A}R^{16A} [wherein

R^{15A} and R^{16A} are the same or different and each represents

a hydrogen atom, hydroxy, lower alkyl, or

substituted lower alkyl (in said substituted lower alkyl, the substituents (a) are the same or different and 1 to 3 substituent(s), such as hydroxy, lower alkoxy, oxo, carboxy, lower alkoxy carbonyl, aryl, a heterocyclic group, amino, lower alkylamino, di(lower alkyl)amino and the like), or

R^{15A} and R^{16A} are combined to form a heterocyclic group

together with the adjacent nitrogen atom],

-NR⁴¹R⁴² [wherein

R⁴¹ and R⁴² are the same or different and each represents

a hydrogen atom, lower alkyl,

lower alkanoyl, aroyl, aryl,

a heterocyclic group,

substituted lower alkyl (the substituent in said substituted lower alkyl has the same meaning as that of the aforementioned substituent (a) in the substituted lower alkyl),

a substituted lower alkanoyl (in said substituted lower alkanoyl, the substituents (b) are the same or different and 1 to 3 substituent(s), such as hydroxy, lower alkoxy, oxo, carboxy, lower alkoxy carbonyl, amino, lower alkylamino, di(lower alkyl)amino and the like),

substituted aroyl (the substituent in said substituted aroyl has the same meaning as that of the aforementioned substituent (b) in the substituted lower alkanoyl),

substituted aryl (the substituent in said substituted aryl has the same meaning as that of the after-mentioned substituent (xii) in the substituted aryl) or

a substituted heterocyclic group (the substituent in said substituted heterocyclic group has the same meaning as that of the after-mentioned substituent (xiii) in the substituted heterocyclic group), or

R⁴¹ and R⁴² are combined to form a heterocyclic group or a substituted heterocyclic group together with the adjacent nitrogen atom (the substituent in said substituted heterocyclic group formed together with the adjacent nitrogen atom has the same meaning as that of the after-mentioned substituent (xiii) in the substituted heterocyclic group formed together with the adjacent nitrogen atom))), or

R¹⁵ and R¹⁶ are combined to form a heterocyclic group or a substituted heterocyclic group together with the adjacent nitrogen atom (the substituent in said substituted heterocyclic group formed together with the adjacent nitrogen atom has the same meaning as that of the after-mentioned substituent (xiii) in the substituted heterocyclic group formed together with the adjacent nitrogen atom)>,
-CO₂R²⁶ [wherein

R^{26} represents
 a hydrogen atom, lower alkyl, cycloalkyl, lower alkenyl,
 lower alkynyl, aryl,
 substituted aryl (the substituent in said substituted aryl has the same meaning as that of the after-mentioned
 5 substituent (xi) in the substituted aryl), or
 substituted lower alkyl [in said substituted lower alkyl, the substituents (c) are the same or different and 1
 to 3 substituent(s), such as
 hydroxy, halogen, lower alkoxy, oxo, carboxy,
 lower alkoxycarbonyl, aryl, a heterocyclic group,
 10 $-CONR^{15B}R^{16B}$ (wherein R^{15B} and R^{16B} have the same meanings as those of the aforementioned R^{15}
 and R^{16} , respectively),
 $-NR^{41A}R^{42A}$ (wherein R^{41A} and R^{42A} have the same meanings as those of the aforementioned R^{41} and
 R^{42} , respectively), and the like]],
 $-COR^{26A}$ (wherein R^{26A} has the same meaning as that of the aforementioned R^{26}),
 15 $-NR^{17}R^{18}$ (wherein
 R^{17} and R^{18} are the same or different and each represents
 a hydrogen atom, lower alkyl, lower alkenyl, aryl,
 aryl, a heterocyclic group, cycloalkyl,
 aralkyloxycarbonyl,
 20 substituted lower alkyl (in said substituted lower alkyl, the substituents (d) are the same or different and 1
 to 3 substituent(s), such as
 hydroxy, lower alkoxy, oxo, carboxy,
 lower alkoxycarbonyl, aryl, a heterocyclic group,
 substituted aryl (the substituent in said substituted aryl has the same meaning as that of the after-
 25 mentioned substituent (xii) in the substituted aryl),
 a substituted heterocyclic group (the substituent in said substituted heterocyclic group has the same
 meaning as that of the after-mentioned substituent (xiii) in the substituted heterocyclic group),
 $-O(CH_2CH_2O)_nR^{19}$ (wherein n represents an integer of from 1 to 15, and R^{19} represents lower alkyl),
 $-CONR^{15C}R^{16C}$ (wherein R^{15C} and R^{16C} have the same meanings as those of the aforementioned R^{15}
 30 and R^{16} , respectively),
 $-SO_2R^{24}$ [wherein
 R^{24} represents
 lower alkyl, aryl or
 substituted aryl (the substituent in said substituted aryl has the same meaning as that of the
 35 after-mentioned substituent (xii) in the substituted aryl)],
 $-NR^{41B}R^{42B}$ (wherein R^{41B} and R^{42B} have the same meanings as those of the aforementioned R^{41} and
 R^{42} , respectively), and the like),
 substituted aryl (the substituent in said substituted aryl has the same meaning as that of the after-mentioned
 substituent (xii) in the substituted aryl),
 40 a substituted heterocyclic group (the substituent in said substituted heterocyclic group has the same mean-
 ing as that of the after-mentioned substituent (xii) in the substituted heterocyclic group),
 $-COR^{26B}$ (wherein
 R^{26B} represents
 lower alkyl, lower alkenyl, lower alkynyl,
 45 aryl,
 substituted lower alkyl (the substituent in said substituted lower alkyl has the same meaning as
 that of the aforementioned substituent (c) in the substituted lower alkyl),
 substituted aryl (the substituent in said substituted aryl has the same meaning as that of the after-
 mentioned substituent (xii) in the substituted aryl),
 50 $-NR^{26C}R^{26D}$ (wherein R^{26C} and R^{26D} are the same or different, and each has the same meaning
 as that of the aforementioned R^{26}) or
 $-OR^{27}$ [wherein
 R^{27} represents
 lower alkyl, aryl,
 55 substituted lower alkyl (the substituent in said substituted lower alkyl has the same meaning
 as that of the aforementioned substituent (c) in the substituted lower alkyl) or
 substituted aryl (the substituent in said substituted aryl has the same meaning as that of
 the after-mentioned substituent (xii) in the substituted aryl)], or

- $\text{SO}_2\text{R}^{26\text{E}}$ (wherein $\text{R}^{26\text{E}}$ has the same meaning as that of the aforementioned R^{26}), or

R^{17} and R^{18} are combined to form a heterocyclic group or a substituted heterocyclic group together with the adjacent nitrogen atom (the substituent in said substituted heterocyclic group formed together with the adjacent nitrogen atom has the same meaning as that of the after-mentioned substituent (xlii) in the substituted heterocyclic group formed together with the adjacent nitrogen atom)>.

- $\text{N}^+\text{R}^{20}\text{R}^{21}\text{R}^{22}\text{X}^-$ (wherein

R^{20} and R^{21} are the same or different and each represents lower alkyl, or R^{20} and R^{21} are combined to form a heterocyclic group together with the adjacent nitrogen atom,

R^{22} represents lower alkyl, and

X represents each atom of chlorine, bromine or iodine),

- OR^{23} (wherein

R^{23} represents

lower alkyl, cycloalkyl, aryl, a heterocyclic group,

substituted aryl (the substituent in said substituted aryl has the same meaning as that of the after-mentioned substituent (xii) in the substituted aryl),

a substituted heterocyclic group (the substituent in said substituted heterocyclic group has the same meaning as that of the after-mentioned substituent (xiii) in the substituted heterocyclic group),

substituted lower alkyl (in said substituted lower alkyl, the substituents (e) are the same or different and 1 to 3 substituent(s), such as

hydroxy, halogen, lower alkoxy, oxo, carboxy,

lower alkoxy carbonyl, aryl, a heterocyclic group,

substituted aryl (the substituent in said substituted aryl has the same meaning as that of the after-mentioned substituent (xii) in the substituted aryl),

a substituted heterocyclic group (the substituent in said substituted heterocyclic group has the same meaning as that of the after-mentioned substituent (xiii) in the substituted heterocyclic group),

- $\text{O}(\text{CH}_2\text{CH}_2\text{O})_{\text{nA}}\text{R}^{19\text{A}}$ (wherein nA and $\text{R}^{19\text{A}}$ have the same meanings as those of the aforementioned n and R^{19} , respectively),

- $\text{CONR}^{15\text{D}}\text{R}^{16\text{D}}$ (wherein $\text{R}^{15\text{D}}$ and $\text{R}^{16\text{D}}$ have the same meanings as those of R^{15} and R^{16} , respectively);

- $\text{NR}^{41\text{C}}\text{R}^{42\text{C}}$ (wherein $\text{R}^{41\text{C}}$ and $\text{R}^{42\text{C}}$ have the same meanings as those of the aforementioned R^{41} and R^{42} , respectively) and the like],

- $\text{COR}^{26\text{F}}$ (wherein $\text{R}^{26\text{F}}$ has the same meaning as that of the aforementioned R^{26}) or

- $\text{CONR}^{15\text{E}}\text{R}^{16\text{E}}$ (wherein $\text{R}^{15\text{E}}$ and $\text{R}^{16\text{E}}$ have the same meanings as those of the aforementioned R^{15} and R^{16} , respectively)),

- $\text{SR}^{23\text{A}}$ (wherein $\text{R}^{23\text{A}}$ has the same meaning as that of the aforementioned R^{23}),

- SO_2R^{25} (wherein

R^{25} represents

lower alkyl, cycloalkyl, aryl,

substituted lower alkyl (the substituent in said substituted lower alkyl has the same meaning as that of the aforementioned substituent (c) in the substituted lower alkyl),

a substituted aryl (the substituent in the substituted aryl has the same meaning as that of the after-mentioned substituent (xii) in the substituted aryl), or

- $\text{NR}^{15\text{F}}\text{R}^{16\text{F}}$ (wherein $\text{R}^{15\text{F}}$ and $\text{R}^{16\text{F}}$ have the same meanings as those of the aforementioned R^{15} and R^{16} , respectively)),

- $\text{OSO}_2\text{R}^{25\text{A}}$ (wherein $\text{R}^{25\text{A}}$ has the same meaning as that of the aforementioned R^{25}), and the like.

Herein, the lower alkyl moiety in the lower alkyl, the lower alkoxy, the lower alkoxy carbonyl, the lower alkylamino and the di(lower alkyl)amino, the aryl moiety in the aryl and the aroyl, the cycloalkyl, the lower alkenyl, the lower alkynyl, the heterocyclic group, and the heterocyclic group formed together with the adjacent nitrogen atom have the same meanings as those of the aforementioned lower alkyl (i), aryl (v), cycloalkyl (ii), lower alkenyl (iii), lower alkynyl (iv), heterocyclic group (vi) and a heterocyclic group formed together with the adjacent nitrogen atom (vii), respectively. Also, the lower alkyl moiety in the lower alkanoyl mentioned here has the same meaning as that of the aforementioned lower alkyl (i), the halogen (ix) represents each atom of fluorine, chlorine, bromine and iodine, and examples of the aralkyl moiety (xi) in the aralkyloxycarbonyl include aralkyl having 7 to 15 carbon atoms, for example, benzyl, phenethyl, benzhydryl, naphthylmethyl and the like.

(xii) The substituents in the substituted aryl, the substituted aryloxy, the substituted arylamino and the substituted phenylene may be the same or different and 1 to 3 substituent(s), such as

halogen, lower alkyl, nitro, oxo, hydroxy, lower alkoxy, amino, lower alkylamino, di(lower alkyl)amino, lower alkylaminocarbonyloxy, di(lower alkyl)aminocarbonyloxy, lower alkanoyl, lower alkanoylamino, lower alkanoyloxy,

aryl, arylsulfonyl, heterocyclic amino, aroyl, carboxy, lower alkoxycarbonyl, cyano, methylenedioxy,

substituted lower alkyl (in said substituted lower alkyl, the substituents (f) are the same or different and 1 to 3 substituent(s), such as halogen, oxo, carboxy, lower alkoxycarbonyl, amino, lower alkylamino, di(lower alkyl)amino, hydroxy, lower alkoxy and the like),

substituted arylsulfonyl (the substituent in said substituted arylsulfonyl has the same meaning as that of the aforementioned substituent (f)),

substituted heterocyclic amino (the substituent in said substituted heterocyclic amino has the same meaning as that of the aforementioned substituent (f)) and the like.

the lower alkyl moiety in the lower alkyl, the lower alkylamino, the di(lower alkyl)amino, the lower alkylamino-carbonyloxy, the di(lower alkyl)aminocarbonyloxy (the two lower alkyl moieties in said di(lower alkyl)aminocarbonyloxy may be the same or different), the lower alkoxycarbonyl and the lower alkoxy, the heterocyclic moiety in the heterocyclic amino, the aryl moiety in the aryl, the arylsulfonyl and the aroyl, and the halogen have the same meanings as those of the aforementioned lower alkyl (i), heterocyclic group (vi), aryl (v) and halogen (ix), respectively. Also, examples of the lower alkanoyl moiety (x) in the lower alkanoyl, the lower alkanoylamino and the lower alkanoyloxy which are noted here include a straight or branched chain alkanoyl having 2 to 9 carbon atoms, for example, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl, nonanoyl and the like.

(xiii) Examples of the substituent in the substituted heterocyclic group and the substituted heterocyclic group formed together with the adjacent nitrogen atom include oxo and the like as well as the aforementioned groups mentioned in the definition of the substituent (xi) in the substituted aryl.

[0008] Example of the pharmacologically acceptable salt of Compound (I) and Compound (IA) include pharmacologically acceptable acid addition salts, metal salts, ammonium salts, organic amine addition salts, amino acid addition salts and the like. Examples of the acid addition salt include an inorganic salt such as a hydrochloride, a sulfate and a phosphate, an organic acid salt such as an acetate, a maleate, a fumarate, a tartrate, a citrate, a lactate, an aspartate, a glutamate, succinate and the like. Examples of the metal salt include an alkali metal salt such as a sodium salt and a potassium salt, an alkaline-earth metal salt such as a magnesium salt and a calcium salt, an aluminium salt, a zinc salt and the like. Examples of the ammonium salt include a salt of ammonium, tetramethylammonium and the like. Examples of the organic amine addition salt include an addition salt with morpholine, piperidine or the like. Examples of the amino acid addition salt include an addition salt with lysine, glycine, phenylalanine and the like.

[0009] Next, the methods of preparing the Compound (I) and the Compound (IA) are described as follows.

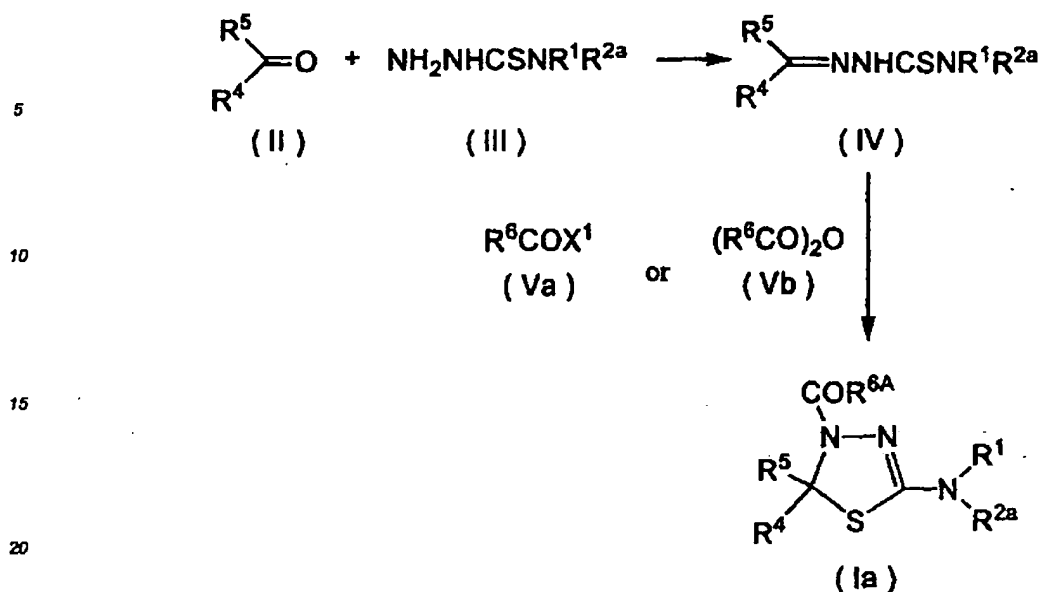
[0010] In the preparing methods as shown below, when the defined group changes under the conditions of the method carried out, or the method is inappropriate for carrying out, the desired compound can be obtained by using the protection and deprotection of the groups which are ordinarily used in the synthetic organic chemistry [e.g., Protective Groups in Organic Synthesis, T. W. Greene, John Wiley & Sons Inc. (1981)] and the like. In addition, the order of the steps for introducing a substituent and the like may be changed, if necessary.

[0011] Compound (I) can be prepared according to the following reaction steps.

[0012] Compound (IA) can also be prepared in the similar manner as in the preparing methods of Compound (I) as shown below.

Preparing method 1

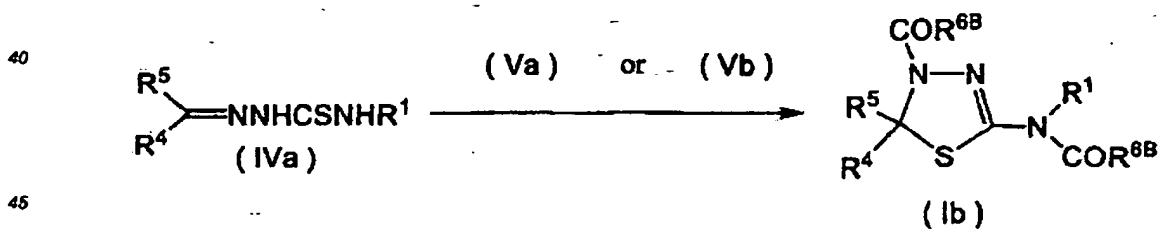
[0013] Among Compound (I), Compound (Ia) wherein R² is a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted cycloalkyl, or R¹ and R² are combined to form a substituted or unsubstituted heterocyclic group together with the adjacent nitrogen atom, and R³ is -C(=O)R^{6A} can be obtained from Compound (II) and Compound (III), via Compound (IV), in accordance with known methods [e.g., J. Heterocyclic Chem., Vol. 21, p. 599 (1984) and the like]:



(wherein R^1 , R^4 , R^5 , R^6 and R^{6A} have the same meanings as those mentioned above, respectively, X^1 has the same meaning as that of the aforementioned X , and R^{2a} represents a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted cycloalkyl among the definition of the aforementioned R^2 , or R^1 and R^{2a} are combined to form a substituted or unsubstituted heterocyclic group together with the adjacent nitrogen atom.)

Preparing method 2

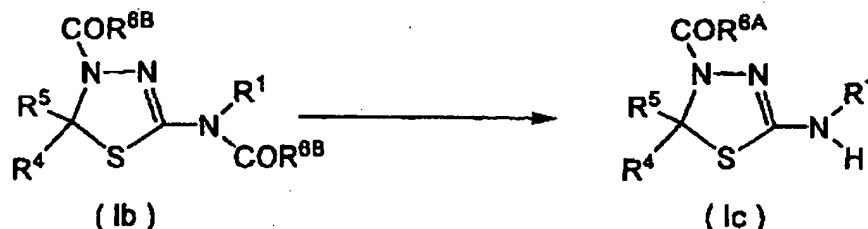
[0014] Among Compound (I), Compound (Ib) wherein R^2 and R^3 are the same to be $-\text{C}(=\text{O})\text{R}^{6B}$ (wherein R^{6B} has the same meaning as that of the aforementioned R^6) can be obtained from Compound (IVa) among Compound (IV) prepared by the preparing method 1 wherein R^{2a} is a hydrogen atom, and Compound (Va) or Compound (Vb) in accordance with known methods [e.g., J. Bangladesh Chem. Soc., Vol. 5, p. 127 (1992), J. Org. Chem., Vol. 45, p. 1473 (1980), Patent of East Germany No. 243930, and the like]:



(wherein R^1 , R^4 , R^5 and R^{6B} have the same meanings as those mentioned above, respectively.)

Preparing method 3

[0015] Among Compound (Ia), Compound (Ic) wherein R^2 is a hydrogen atom and R^3 is $-\text{C}(=\text{O})\text{R}^{6A}$ can be obtained by the following step from Compound (Ib) prepared by the Preparing method 2:



(wherein R^1 , R^4 , R^5 , R^{6A} and R^{6B} have the same meanings as those mentioned above, respectively.)

[0016] Compound (Ic) can be obtained by treatment of Compound (Ib) in an inert solvent, for example, N,N-dimethylformamide and the like, in the presence of an appropriate base such as sodium hydride and the like, at a temperature between 0°C and 80°C for 10 minutes to 10 hours. The base is preferably used in an amount of 1 to 5 equivalents to Compound (Ib).

[0017] Alternatively, Compound (Ic) can also be obtained by the following method.

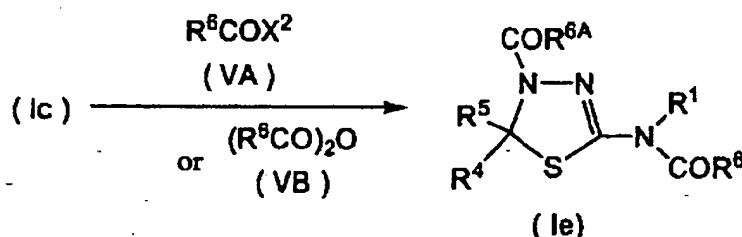
[0018] Compound (Ic) can be obtained by treatment of Compound (Ib) in an inert solvent, for example, aqueous or anhydrous ethanol, acetonitrile, chloroform and the like, in the presence of an appropriate base such as hydrazine monohydrate, aqueous sodium hydroxide and the like, at a temperature between 0°C and 50°C for 1 to 10 hours. The base is preferably used in an amount of 2 to 10 equivalents to Compound (Ib).

[0019] Compound (Ic) can also be obtained by the following method.

[0020] Compound (Ic) can be obtained by treatment of Compound (Ib) in a solvent such as methanol, tert-butanol and the like, in the presence of a reducing agent such as sodium borohydride and the like, and if necessary, in the presence of cerium chloride heptahydrate and the like, at a temperature between -10°C and 100°C for 0.1 to 15 hours. The reducing agent is preferably used in an amount of 1 to 200 equivalents to Compound (Ib).

Preparing method 4

[0021] Among Compound (I), Compound (Ie) wherein R^2 is $-\text{C}(=\text{O})\text{R}^6$ and R^3 is $-\text{C}(=\text{O})\text{R}^{6A}$ can be obtained by the following step from Compound (Ic) obtained by the Preparing method 1 or 3.

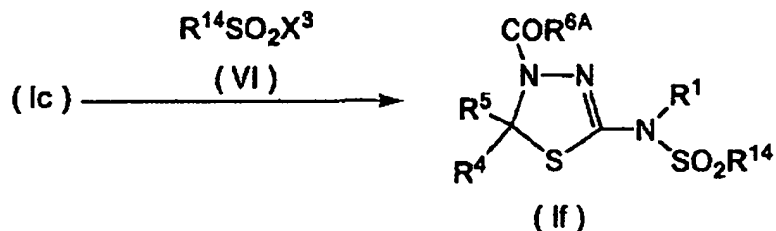


(wherein R^1 , R^4 , R^5 , R^6 and R^{6A} have the same meanings as those mentioned above, respectively, and X^2 has the same meaning as that of the aforementioned X.)

[0022] Compound (Ie) can be obtained by allowing Compound (Ic) to react with Compound (VA) or Compound (VB) in an inert solvent, for example, acetone, ethyl acetate, acetonitrile, N,N-dimethylformamide, dichloromethane and the like, in the presence of an appropriate base such as pyridine, 4-(dimethylamino)pyridine (DMAP), sodium hydride and the like, at a temperature between 0°C and 120°C for 2 to 12 hours. The base and Compound (VA) or Compound (VB) are preferably used, respectively, in an amount of 1 to 3 equivalents to Compound (Ic).

Preparing method 5

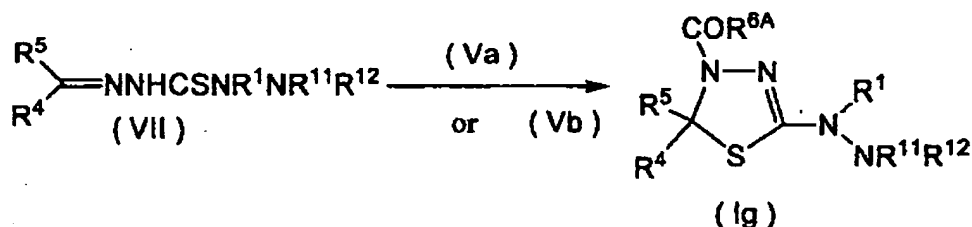
[0023] Among Compound (I), Compound (If) wherein R^2 is $-\text{SO}_2\text{R}^{14}$ and R^3 is $-\text{C}(=\text{O})\text{R}^{6A}$ can be obtained from Compound (Ic) prepared by the Preparing method 1 or 3 in accordance with the method described in for example, Shin-Jikken-Kagaku-Koza (New Experiment Chemistry Lecture) Vol. 14, p. 1803 (Maruzen, 1978):



(wherein R^1 , R^4 , R^5 , R^{6A} and R^{14} have the same meanings as those mentioned above, respectively, and X^3 has the same meaning as that of the aforementioned X .)

Preparing method 6

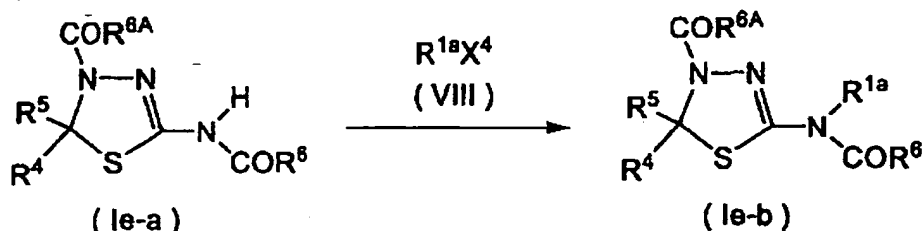
[0024] Among Compound (I), Compound (Ig) wherein R^2 is $-NR^{11}R^{12}$ and R^3 is $-C(=O)R^{6A}$ can be obtained from Compound (VII) prepared in accordance with the method described in Indian J. Chem., Section B, Vol. 31(B), p. 547 (1992) in accordance with the methods described in for example, Indian J. Chem., Section B, Vol. 31B(8), p. 547 (1992), Phosphorus Sulfur & Silicon & the Related Elements, Vol. 122, p. 307 (1997) and the like,:



(wherein R^1 , R^4 , R^5 , R^{6A} , R^{11} and R^{12} have the same meanings as those mentioned above, respectively.)

Preparing method 7

[0025] Among Compound (Ie), Compound (Ie-b) wherein R^1 is substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted cycloalkyl can be obtained by the following step from Compound (Ie-a) among Compound (Ie) wherein R^1 is a hydrogen atom prepared by the Preparing method 4:



(wherein R^4 , R^5 , R^6 and R^{6A} have the same meanings as those mentioned above, respectively, X^4 has the same meaning as that of the aforementioned X , and R^{1a} represents substituted or unsubstituted lower alkyl, a substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted cycloalkyl among the definition of the aforementioned R^1 .)

[0026] Compound (Ie-b) can be obtained by allowing Compound (Ie-a) to react with Compound (VIII) in an inert solvent, for example, N,N-dimethylformamide and the like, in the presence of an appropriate base such as sodium hydroxide, at a temperature between 0°C and room temperature for 1 to 24 hours. The base and Compound (VIII) are preferably used in amounts of 2 to 5 equivalents and 2 to 3 equivalents, respectively, to Compound (Ie-a).

Preparing method 8

[0027] Among Compound (I), Compound (Ih) wherein R^3 is a hydrogen atom can be obtained by the methods described in for example, Phosphorus, Sulfur and Silicone and the Related Elements, Vol. 122, p. 307 (1997) and Chem. Ber., Vol. 123, p. 691 (1990) and the like, or the methods similar to the aforementioned methods.

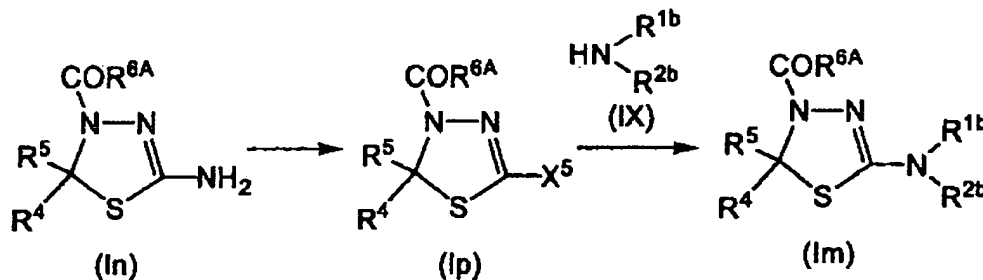
Preparing method 9

[0028] Among Compound (I), Compound (Ij) wherein R^2 and/or R^3 is $-C(=S)R^6$ and/or $-C(=S)R^{6A}$, respectively, can be obtained by thiocarbonylation of Compound (Ik) wherein the corresponding R^2 and/or R^3 is $-C(=O)R^6$ and/or $-C(=O)R^{6A}$, respectively, among Compound (Ia) to Compound (Ih) obtained by the aforementioned the Preparing methods 1 to 7.

[0029] For example, Compound (Ij) can be obtained by treatment of Compound (Ik) in a solvent such as toluene and tetrahydrofuran, with an appropriate thiocarbonylating agent such as 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphethane-2,4-disulfide (Lawesson's reagent), phosphorus pentasulfide and the like, at a temperature between room temperature and the boiling point of the solvent for 1 to 24 hours. The thiocarbonylating agent is preferably used in an amount of 2 to 10 equivalents to Compound (Ik).

Preparing method 10

[0030] Among Compound (I), Compound (Im) wherein R^3 is $-C(=O)R^{6A}$ and R^1 and R^2 are combined to form a substituted or unsubstituted heterocyclic group together with the adjacent nitrogen atom can be obtained by the following step from Compound (In) wherein R^1 and R^{2a} are hydrogen atoms among Compound (Ia) prepared by the Preparing method 1, or from Compound (In) wherein R^1 is a hydrogen atom among Compound (Ic) prepared by the Preparing method 3:



(wherein R^4 , R^5 and R^{6A} have the same meanings as those mentioned above, respectively, X^5 has the same meaning as that of the aforementioned X , R^{1b} and R^{2b} represent a substituted or unsubstituted heterocyclic group formed together with the adjacent nitrogen atom, said heterocyclic group formed together with the adjacent nitrogen atom has the same meaning as that of the aforementioned heterocyclic group (vii) formed together with the adjacent nitrogen atom, and the substituent in said substituted heterocyclic group formed together with the adjacent nitrogen atom has the same meaning as that of the aforementioned substituent (xiii) in the heterocyclic group.)

[0031] Compound (Ip) can be obtained from Compound (In) by the methods described in for example, Chem. Commun., Vol. 8, p. 873 (1998) and the like, or the methods similar to the aforementioned methods.

[0032] Compound (Im) can be obtained by allowing Compound (Ip) to react with Compound (IX) in an inert solvent, for example, dichloromethane and the like, at a temperature between 0°C and 64°C for 10 minutes to 24 hours. Compound (IX) is preferably used in an amount of 2 to 50 equivalents to Compound (Ip).

[0033] Alternatively, Compound (Im) can also be obtained from Compound (Ie-c) wherein R^1 is a hydrogen atom and R^6 is an alkyl group substituted with carboxyl group among Compound (Ie) prepared by the Preparing method 4 by the method described in for example, Synthesis-Stuttgart, Vol. 5, p. 420 (1991) or the methods similar to the aforementioned method.

[0034] Moreover, Compound (Im) can also be obtained from Compound (Ie-d) wherein R^1 is a hydrogen atom and R^6 is an alkyl group substituted with halogen among Compound (Ie) by the method described in for example, Shin-Jikken-Kagaku-Koza (New Experiment Chemistry Lecture) Vol. 14, p. 1174 (Maruzen, 1978) and the like, or the methods similar to the aforementioned methods.

[0035] Furthermore, among Compound (I), Compound (Ij-a) wherein R^3 is $-C(=S)R^{6A}$ and R^1 and R^2 are combined

to form a substituted or unsubstituted heterocyclic group together with the adjacent nitrogen atom can be obtained from Compound (Im) in the similar manner as the aforementioned the Preparing method 9.

[0036] In Compound (I), conversion of the functional group contained in R¹, R², R³, R⁴ or R⁵ can also be carried out by the aforementioned steps, or also by the other known methods [e.g., Comprehensive Organic Transformations, R. C. Larock (1989) and the like].

[0037] Compound (I) having the desired functional group at the desired position can be obtained by carrying out the aforementioned methods in appropriate combination.

[0038] The intermediates and the objective compounds in the aforementioned preparation methods can be purified and isolated by conducting a purification method ordinarily used in the synthetic organic chemistry such as filtration, extraction, washing, drying, concentration, recrystallization, various chromatography such as high performance liquid chromatography, thin layer chromatography, silica gel chromatography and the like. The intermediates can also be subjected to the next reaction without particular purification.

[0039] Some compounds among Compounds (I) may exist as position isomers, geometrical isomers, optical isomers, tautomers and the like. All possible isomers including the aforementioned isomers and mixtures thereof can be used for the antitumor agent of the present invention.

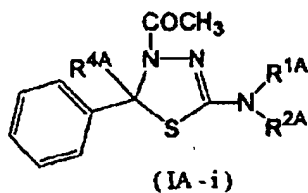
[0040] To obtain a salt of Compound (I), when Compound (I) obtained as a salt form, it may be purified as it is. When Compound (I) obtained as a free form, it may be dissolved or suspended in an appropriate solvent, and added with an appropriate acid or base to form a salt and then be isolated.

[0041] In addition, Compound (I) or a pharmacologically acceptable salt thereof may exist in the form of adducts with water or variety of solvents, which also can be used for the antitumor agent of the present invention.

[0042] Specific examples of Compound (IA) obtained by the present invention are shown in Tables 1 to 10. However, the compounds of the present invention are not limited to these examples.

[0043] The compounds shown in Tables 1 to 10 are used for the antitumor agent of the present invention, and other than the compounds, specific examples of compounds used in the present invention are shown in Tables 11 to 13. However, the compound used in the present invention is not limited to these examples.

Table 1



Example No.	Compound No.	R ^{1A}	R ^{2A}	R ^{4A}
2	2	-H	-COCH ₃	-CH ₂ CH ₃
4	4	-H	-COCH ₃	-CH(CH ₃) ₂
5	5	-H	-COCH ₃	
7	7	-CH ₃	-COCH ₃	-CH ₃
8	8	-CH ₂ CH ₃	-CH ₂ CH ₃	-CH ₃
8	9	-CH ₂ CH ₃	-COCH ₃	-CH ₃
9	10	-(CH ₂) ₂ CH ₃	-(CH ₂) ₂ CH ₃	-CH ₃
9	11	-(CH ₂) ₂ CH ₃	-COCH ₃	-CH ₃
129	136	-H	-CO ₂ C(CH ₃) ₃	-CH ₃
130	137	-H	-CON(CH ₃) ₂	-CH ₃
131	138			-CH ₃
132	139			-CH ₃
133	140	-H	-CO(CH ₂) ₄ CH ₃	-CH ₂ NHSO ₂ CH ₃
134	141	-H	-COCH=CHCH ₃	-CH ₂ NHSO ₂ CH ₃
135	142	-H		-CH ₂ NHSO ₂ CH ₃
136	143	-H	-COC(CH ₃) ₂ OCOCH ₃	-CH ₂ NHSO ₂ CH ₃
137	144	-H	-COC(CH ₃) ₂ OH	-CH ₂ NHSO ₂ CH ₃
138	145	-H	-COCH ₂ OCH ₃	-CH ₂ NHSO ₂ CH ₃

Table 1 (Continued)


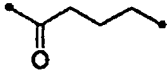

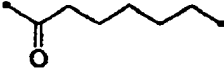
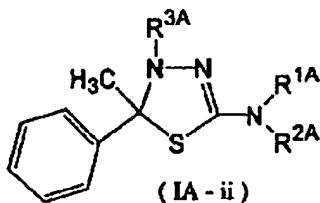
Example No.	Compound No.	R ^{1A}	R ^{2A}	R ^{4A}
139	146	-H	-COCH ₂ Cl	-CH ₂ NHSO ₂ CH ₃
140	147	-H	-COCH ₂ N(CH ₃) ₂	-CH ₂ NHSO ₂ CH ₃
141	148	-H	-CO(CH ₂) ₃ CO ₂ CH ₃	-CH ₂ NHSO ₂ CH ₃
142	149	-H	-CO(CH ₂) ₃ CO ₂ H	-CH ₂ NHSO ₂ CH ₃
143	150			-CH ₂ NHSO ₂ CH ₃
144	151	-H	-CO(CH ₂) ₃ Br	-CH ₂ NHSO ₂ CH ₃
145	152			-CH ₂ NHSO ₂ CH ₃
146	153	-H	-CO(CH ₂) ₄ Br	-CH ₂ NHSO ₂ CH ₃
147	154			-CH ₂ NHSO ₂ CH ₃
148	155	-H	-CO(CH ₂) ₅ Br	-CH ₂ NHSO ₂ CH ₃
149	156			-CH ₂ NHSO ₂ CH ₃

Table 2



Example No.	Compound No.	R ^{1A}	R ^{2A}	R ^{3A}
10	12	-CH ₂ Ph	-CH ₂ Ph	-COCH ₃
10	13	-CH ₂ Ph	-COCH ₃	-COCH ₃
12	15	-CH ₃	-H	-COCH ₃
13	16	-CH ₃	-CH ₃	-COCH ₃
14	17	-CH ₃	-H	-COCH ₂ CH ₃
15	18	-CH ₃	-COCH ₃	-COCH ₂ CH ₃
16	19	-CH ₃	-COCH ₂ CH ₃	-COCH ₂ CH ₃
17	20	-CH ₃	-CO(CH ₂) ₂ CH ₃	-CO(CH ₂) ₂ CH ₃
18	21	-CH ₃	-COCH(CH ₃) ₂	-COCH(CH ₃) ₂
76	79	-CH ₂ CH=CH ₂	-COCH ₃	-COCH ₃
77	80	-CH ₂ CH=CH ₂	-H	-COCH(CH ₃) ₂
77	81	-CH ₂ CH=CH ₂	-COCH ₃	-COCH(CH ₃) ₂
78	82	-H	-COC(CH ₃) ₃	-COC(CH ₃) ₃
79	83	-CH ₃	-H	-COCH(CH ₃) ₂
79	84	-CH ₃	-COCH ₃	-COCH(CH ₃) ₂
80	85	-H	-COCH(CH ₃) ₂	-COCH(CH ₃) ₂
81	86	-H	-H	-COCH(CH ₃) ₂
81	87	-H	-COCH ₃	-COCH(CH ₃) ₂

* Ph: phenyl

Table 2 (Continued)

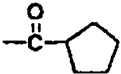
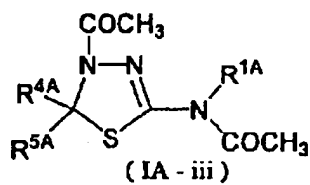
Example No.	Compound No.	R ^{1A}	R ^{2A}	R ^{3A}
82	88	-H	-COCH(CH ₃) ₂	-COCH ₃
83	89	-H		-COCH ₃
84	90	-H	-H	-COCH ₂ CH(CH ₃) ₂
84	91	-H	-COCH(CH ₃) ₂	-COCH ₂ CH(CH ₃) ₂
85	92	-H	-COCH ₃	-COC(CH ₃) ₃
86	93	-H	-COC(CH ₃) ₃	-COCH ₃

Table 3



Example No.	Compound No.	R ^{1A}	R ^{4A}	R ^{5A}
22	25	-H	-CH ₃	-CH=CHPh
23	26	-H	-(CH ₂) ₃ CH ₃	-(CH ₂) ₃ CH ₃
24	27	-H		
25	28	-H		
26	29	-H		
28	31	-H		
29	32	-H	-CH ₃	
30	33	-H	-CH ₃	
31	34	-H	-CH ₃	
32	35	-H	-CH ₃	
33	36	-H	-CH ₃	
34	37	-H	-CH ₃	
35	38	-H	-CH ₃	

* Ph: phenyl

Table 3 (Continued)

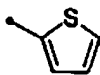
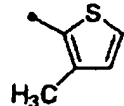
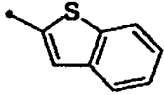
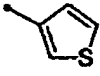
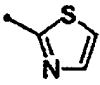
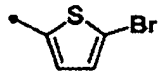
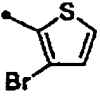
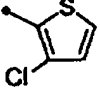
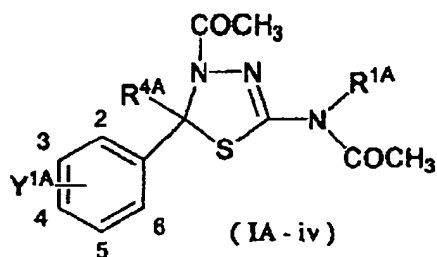
Example No.	Compound No.	R ^{1A}	R ^{4A}	R ^{5A}
38	41	-CH ₂ CH ₃	-CH ₃	
39	42	-H	-CH ₃	
40	43	-H	-CH ₃	
41	44	-H	-CH ₃	
42	45	-H	-CH ₃	
125	132	-H	-CH ₃	
126	133	-H	-CH ₃	
127	134	-H	-CH ₃	

Table 4

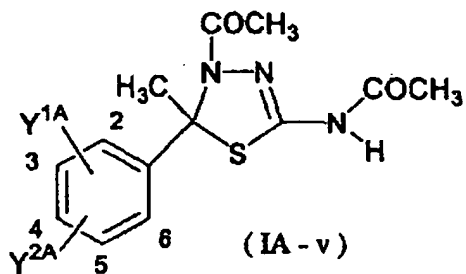


Example No.	Compound No.	R ^{1A}	R ^{4A}	Y ^{1A} (Substituting position)
43	46	-H	-CH ₃	-CH ₃ (2)
44	47	-H	-CH ₃	-CH ₃ (3)
45	48	-H	-CH ₃	-CH ₃ (4)
46	49	-H	-CH ₂ CH ₃	-CH ₂ CH ₃ (2)
47	50	-H	-CH ₃	-OCH ₃ (2)
48	51	-H	-CH ₃	-OCH ₃ (3)
50	53	-H	-CH ₃	-F (2)
51	54	-H	-CH ₃	-F (3)
52	55	-H	-CH ₃	-F (4)
53	56	-H	-CH ₃	-Cl (2)
54	57	-CH ₂ CH ₃	-CH ₃	-Cl (2)
55	58	-H	-CH ₃	-Cl (3)
56	59	-H	-CH ₃	-Cl (4)
57	60	-H	-CH ₃	-Br (2)
58	61	-H	-CH ₃	-OCOCH ₃ (2)
60	63	-H	-H	-OCOCH ₃ (3)
61	64	-H	-CH ₃	-OCOCH ₃ (4)
62	65	-H	-CH ₃	-NO ₂ (2)

Table 4 (Continued)

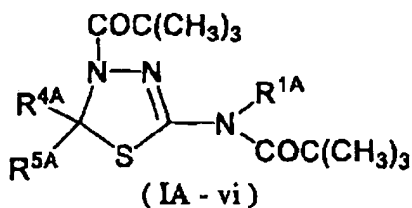
Example No.	Compound No.	R ^{1A}	R ^{4A}	Y ^{1A} (Substituting position)
65	68	-H	-CH ₃	-OH (2)
66	69	-H	-CH ₃	-OH (3)
67	70	-H	-CH ₃	-OH (4)
68	71	-H	-CH ₃	-CN (3)
69	72	-H	-CH ₃	-CN (4)
70	73	-H	-CH ₃	-CF ₃ (3)
71	74	-H	-CH ₃	-COOH (2)
118	125	-CH ₂ CH ₃	-CH ₃	-OCOCH ₃ (3)
119	126	-CH ₂ CH ₃	-CH ₃	-OH (3)
120	127	-H	-CH ₃	-OCONHCH ₂ CH ₃ (3)

Table 5



Example No.	Compound No.	Y ^{1A} (Substituting position)	Y ^{2A} (Substituting position)
72	75	-OCH ₃ (2)	-OCH ₃ (6)
73	76	-OH (3)	-OH (5)
74	77	-OH (3)	-OH (4)
75	78	-CH ₃ (2)	-CH ₃ (4)

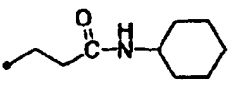
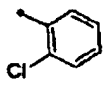
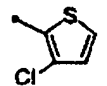
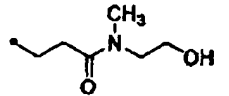
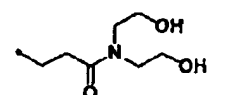
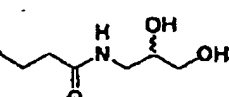
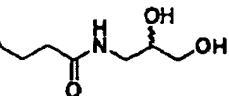
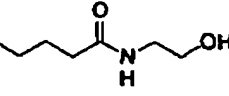
Table 6



Example No.	Compound No.	R ^{1A}	R ^{4A}	R ^{5A}
87	94	-H	-CH ₂ CH ₃	-Ph
88	95	-H	-CH ₂ NHSO ₂ CH ₃	-Ph
89	96	-CH ₃	-CH ₂ NHSO ₂ CH ₃	-Ph
90	97	-H	-CH ₂ NHSO ₂ CH ₂ CH ₃	-Ph
91	98	-H	-CH ₂ OCH ₃	-Ph
92	99	-H	-(CH ₂) ₂ NHSO ₂ CH ₃	-Ph
94	101	-H	-CH ₂ NHCOCF ₃	-Ph
97	104	-H	-(CH ₂) ₂ N(CH ₃) ₂	-Ph
98	105	-H	-(CH ₂) ₂ COOCH ₃	-Ph
99	106	-H	-(CH ₂) ₂ COOH	-Ph
100	107	-H	-(CH ₂) ₂ CONH ₂	-Ph
101	108	-H	-(CH ₂) ₂ CONHOH	-Ph
102	109	-H	-(CH ₂) ₂ CONHCH ₃	-Ph
103	110	-H	-(CH ₂) ₂ CON(CH ₃) ₂	-Ph
104	111	-H	-(CH ₂) ₂ CONH(CH ₂) ₂ OH	-Ph

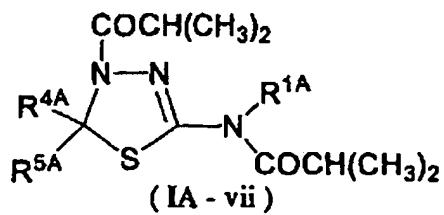
* Ph: phenyl

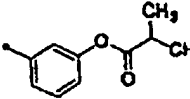
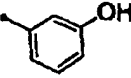

Table 6 (Continued)

Example No.	Compound No.	R ^{1A}	R ^{4A}	R ^{5A}
105	112	-H	$-(CH_2)_2CONH(CH_2)_3CH_3$	-Ph
106	113	-H		-Ph
107	114	-H	$-(CH_2)_3COOCH_3$	-Ph
108	115	-H	$-(CH_2)_3COOH$	-Ph
109	116	-H	$-(CH_2)_3CONHCH_3$	-Ph
110	117	-H	$-(CH_2)_3CONH_2$	-Ph
123	130	-H	$-CH_3$	
128	135	-H	$-CH_3$	
154	161	-H		-Ph
155	162	-H		-Ph
156	163	-H		-Ph
156	164	-H		-Ph
157	165	-H		-Ph
158	166	-H	$-(CH_2)_3OH$	-Ph
159	167	-H	$-(CH_2)_3OSO_2NH_2$	-Ph

* Ph: phenyl, Compound 164: an isomer of Compound 163

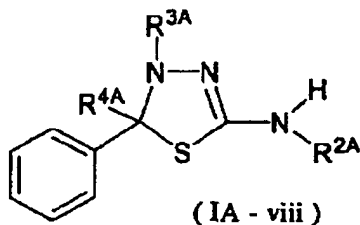
Table 7



Example No.	Compound No.	R ^{1A}	R ^{4A}	R ^{5A}
93	100	-H	-(CH ₂) ₂ NHSO ₂ CH ₃	-Ph
95	102	-COCH(CH ₃) ₂	-CH ₂ NHSO ₂ CH ₃	-Ph
96	103	-H	-CH ₂ NHSO ₂ CH ₃	-Ph
121	128	-H	-CH ₃	
122	129	-H	-CH ₃	
124	131	-H	-CH ₃	

* Ph: phenyl

Table 8



Example No.	Compound No.	R ^{3A}	R ^{3A}	R ^{4A}
111	118	-H	-COCH ₃	-CH ₂ NHSO ₂ CH ₃
112	119	-COC(CH ₃) ₃	-COCH ₃	-CH ₂ NHSO ₂ CH ₃
113	120	-H	-COC(CH ₃) ₃	-CH ₂ NHSO ₂ CH ₃
114	121	-CO(CH ₂) ₅ Br	-COC(CH ₃) ₃	-CH ₂ NHSO ₂ CH ₃
115	122	-CO(CH ₂) ₅ N ₃	-COC(CH ₃) ₃	-CH ₂ NHSO ₂ CH ₃
116	123	-CO(CH ₂) ₅ NH ₂	-COC(CH ₃) ₃	-CH ₂ NHSO ₂ CH ₃
117	124	-CO(CH ₂) ₅ NHCOCH ₃	-COC(CH ₃) ₃	-CH ₂ NHSO ₂ CH ₃
150	157	-H	-COC(CH ₃) ₃	-(CH ₂) ₂ NHSO ₂ CH ₃
151	158	-CO(CH ₂) ₅ Br	-COC(CH ₃) ₃	-(CH ₂) ₂ NHSO ₂ CH ₃
153	160	-COC(CH ₃) ₃	-CSCH ₃	-CH ₂ NHSO ₂ CH ₃
160	168	-COC(CH ₃) ₃	-COCH ₃	-CH ₂ NHSO ₂ CH ₂ Cl
160	169	-COCH ₃	-COCH ₃	-CH ₂ NHSO ₂ CH ₂ Cl
161	170	-COC(CH ₃) ₃	-COCH ₃	-CH ₂ NHSO ₂ CH=CH ₂
161	171	-COC(CH ₃) ₃	-COC(CH ₃) ₃	-CH ₂ NHSO ₂ CH=CH ₂

Table 8 (Continued)

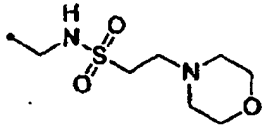
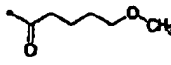

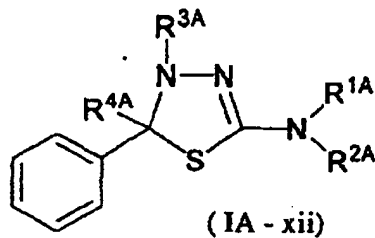
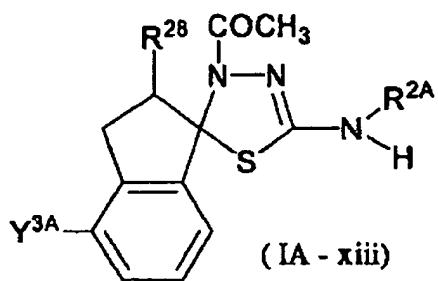
Example No.	Compound No.	R^{2A}	R^{6A}	R^{4A}
162	172	$-\text{COC}(\text{CH}_3)_3$	$-\text{COCH}_3$	
163	173	$-\text{COC}(\text{CH}_3)_2$	$-\text{COCH}_3$	$-\text{CH}_2\text{NHSO}_2(\text{CH}_2)_2\text{NHCH}_2\text{CH}_3$
164	174	$-\text{COC}(\text{CH}_3)_3$	$-\text{COCH}_3$	$-\text{CH}_2\text{NHSO}_2(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$
165	175	$-\text{COC}(\text{CH}_3)_3$	$-\text{COCH}_3$	$-\text{CH}_2\text{NHSO}_2(\text{CH}_2)_2\text{NH}(\text{CH}_2)_2\text{OH}$
166	176	$-\text{COC}(\text{CH}_3)_2$	$-\text{COC}(\text{CH}_3)_3$	$-\text{CH}_2\text{NHSO}_2(\text{CH}_2)_2\text{NHCH}_2\text{CH}_3$
167	177	$-\text{COC}(\text{CH}_3)_3$	$-\text{COC}(\text{CH}_3)_3$	$-\text{CH}_2\text{NHSO}_2(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$
168	178	$-\text{H}$	$-\text{COCH}_3$	$-(\text{CH}_2)_2\text{CO}_2\text{CH}_3$
169	179	$-\text{COC}(\text{CH}_3)_3$	$-\text{COCH}_3$	$-(\text{CH}_2)_2\text{CO}_2\text{CH}_3$
170	180	$-\text{H}$	$-\text{COCH}(\text{CH}_3)_2$	$-(\text{CH}_2)_2\text{NHSO}_2\text{CH}_3$
171	181	$-\text{COC}(\text{CH}_3)_3$	$-\text{COCH}(\text{CH}_3)_2$	$-(\text{CH}_2)_2\text{NHSO}_2\text{CH}_3$
174	184		$-\text{COCH}(\text{CH}_3)_2$	$-(\text{CH}_2)_2\text{NHSO}_2\text{CH}_3$
175	185	$-\text{COCH}_2\text{CH}_3$	$-\text{COCH}_2\text{CH}_3$	$-(\text{CH}_2)_2\text{NHSO}_2\text{CH}_3$
176	186	$-\text{H}$	$-\text{COCH}_2\text{CH}_3$	$-(\text{CH}_2)_2\text{NHSO}_2\text{CH}_3$
177	187	$-\text{COC}(\text{CH}_3)_2$	$-\text{COCH}_2\text{CH}_3$	$-(\text{CH}_2)_2\text{NHSO}_2\text{CH}_3$
180	190	$-\text{H}$	$-\text{COC}(\text{CH}_3)_3$	$-(\text{CH}_2)_2\text{COOCH}_3$
181	191		$-\text{COC}(\text{CH}_3)_3$	$-(\text{CH}_2)_2\text{COOCH}_3$

Table 9



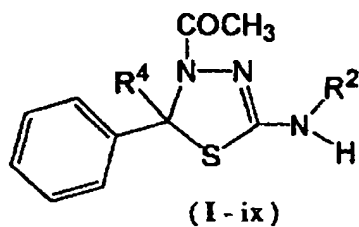
Example Compound		R ^{1A}	R ^{2A}	R ^{3A}	R ^{4A}
No.	No.				
152	159		-COC(CH ₃) ₃		-(CH ₂) ₂ NHSO ₂ CH ₃
172	182		-COCH(CH ₃) ₂		-(CH ₂) ₂ NHSO ₂ CH ₃
173	183		-COCH(CH ₃) ₂		-(CH ₂) ₂ NHSO ₂ CH ₃
178	188		-COCH ₂ CH ₃		-(CH ₂) ₂ NHSO ₂ CH ₃
179	189		-COCH ₂ CH ₃		-(CH ₂) ₂ NHSO ₂ CH ₃
182	192		-COC(CH ₃) ₃		-(CH ₂) ₂ COOCH ₃
183	193		-COC(CH ₃) ₃		-(CH ₂) ₂ COOH
184	194		-COC(CH ₃) ₃		-(CH ₂) ₂ CONH(CH ₂) ₂ OH

Table 10



Example No.	Compound No.	R ^{2A}	R ^{2B}	Y ^{3A}
185	195	-COC(CH ₃) ₃	-OCOCH ₃	-H
186	196	-COC(CH ₃) ₃	-OH	-H
187	197	-H	-H	-OCOCH ₃
188	198	-COC(CH ₃) ₃	-H	-OCOCH ₃
189	199	-COC(CH ₃) ₃	-H	-OH

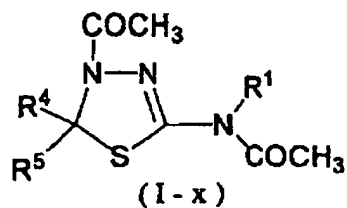
Table 11






Example No.	Compound No.	R ²	R ⁴
1	1	-COCH ₃	-CH ₃
3	3	-COCH ₃	-(CH ₂) ₃ CH ₃
6	6	-COCH ₃	-Ph
11	14	-H	-CH ₃

* Ph: phenyl

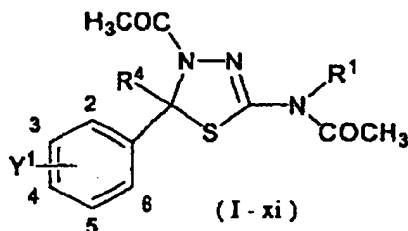
Table 12



Example No.	Compound No.	R ¹	R ⁴	R ⁵
19	22	-H	-CH ₃	-CH ₃
20	23	-H	-CH ₃	-(CH ₂) ₅ CH ₃
21	24	-H	-CH ₃	-(CH ₂) ₂ Ph
27	30	-H		
36	39	-H	-CH ₃	
37	40	-H	-CH ₃	

* Ph: phenyl

Table 13



Example No.	Compound No.	R ¹	R ⁴	Y ¹ (Substituting position)
49	52	-H	-CH ₃	-OCH ₃ (4)
59	62	-H	-CH ₃	-OCOCH ₃ (3)
63	66	-H	-CH ₃	-NO ₂ (3)
64	67	-H	-CH ₃	-NO ₂ (4)

[0044] Next, the pharmacological activity of typical Compounds (I) will be explained by the following test example.

Test example 1: Antiproliferative activity in HCT 116 human colon cancer cells

[0045] HCT 116 cells (ATCC No.: CCL-247) were placed on a 96-well microtiter plate (Nunc, 167008) at a density of 1×10^3 cells/well. The plate was incubated in a 5% CO₂ incubator at 37°C for 24 hours, and then to the plate was added test compounds diluted stepwise to 100 μ L/well in total, and the plate was further incubated in a 5% CO₂ incubator at 37°C for 72 hours. To the culture medium, the XTT (sodium 3'-[1-(phenylaminocarbonyl)-3,4-tetrazolium]-bis(4-methoxy-6-nitro)benzenesulfonic acid hydrate) labeling mixture (Roche Diagnostics, 1465015) was dispensed in 50 μ L/well portions, then the plate was incubated in a 5% CO₂ incubator at 37°C for 1 hour, and the absorbance was measured at 490 nm and 655 nm with a microplate spectrophotometer (Bio-Rad, Model 550).

The inhibitory activity against cell proliferation was shown as a concentration of 50% proliferation inhibition, GI₅₀. GI₅₀ calculation method: The value (difference in absorbance) was calculated by subtracting the absorbance at 655nm from the absorbance at 490nm of each well. The difference in absorbance obtained from the cells untreated with a test compound was defined as 100%, and compared with the difference in absorbance obtained from the cells treated with the solution of the compound in the known concentration, and thereby the concentration of the compound of 50% inhibition against cell proliferation was calculated to obtain GI₅₀.

[0046] The results of the typical compounds obtained in Test example 1 are shown in Table 14. Compounds 138, 152, 165, 170, 173, and 199 showed the GI₅₀ value less than 10 μ mol/L.

Table 14

Compound No.	GI ₅₀ (μ mol/L)
1	1.0
7	0.48
18	0.62
41	0.60
46	0.57
57	0.53
69	0.23
82	0.18

Table 14 (continued)

Compound No.	GI ₅₀ (μmol/L)
99	0.063
104	0.074
107	0.061
134	0.40

[0047] Compound (I) or Compound (IA), or a pharmacologically acceptable salt thereof, per se, can be administered, however, is generally desired to be provided as a form of various pharmaceutical preparations. Also, the pharmaceutical preparations are used for animals or human.

[0048] The pharmaceutical preparations according to the present invention can comprise as an active ingredient Compound (I) or Compound (IA), or a pharmacologically acceptable salt thereof, solely or as a mixture with any other effective ingredient for the treatment. The pharmaceutical preparations are manufactured by mixing the active ingredient with one or more of pharmacologically acceptable carriers using any method well known in the technical field of pharmaceutical science.

[0049] As for administration routes, it is preferred to choose the most effective route for the treatment such as oral administration or parenteral administration, for example, intravenous administration and the like.

[0050] Examples of formulations for administration include tablets, injections and the like.

[0051] Examples of the pharmaceutical carrier used include lactose, mannitol, glucose, hydroxypropyl cellulose, starch, magnesium stearate, sorbitan fatty acid ester, glyceric acid ester, polyvinyl alcohol, distilled water for injection, physiological saline, propylene glycol, polyethylene glycol, ethanol and the like. The pharmaceutical preparation according to the present invention may comprise other various additives such as excipients, lubricants, binders, disintegrator, isotonicities and emulsifiers.

[0052] Compound (I) or Compound (IA), or a pharmacologically acceptable salt thereof is generally administered systemically or locally in the form of an oral or parenteral preparation when used for the aforementioned purpose. The dose and the frequency of administration may vary depending on the administration form, the age and body weight of a patient, nature and severity of the condition to be treated, and the like. Generally, 0.1 to 1,000 mg/kg, preferably 0.5 to 500 mg/kg per single administration for an adult may be administered orally or parenterally, once a day or a few times a day, or may be continuously administered intravenously for 1 to 24 hours a day. However, the dose and the frequency of administration may vary depending on the aforementioned various conditions and the like.

Best Mode for Carrying out the Invention

[0053] The present invention will be explained in detail with reference to the following examples.

[0054] The spectra of proton nuclear magnetic resonance (¹H NMR) used in Examples were measured at 270 or 300 MHz, and exchangeable hydrogen may not always be clearly observed depending on the compound and the measurement conditions. For the descriptions of the multiplicity of signals, those generally applied are used, and the symbol "br" represents an apparent broad signal.

Example 1 (Compound 1)

[0055]

Step 1: Acetophenone (4.00 g, 33.3 mmol) and thiosemicarbazide (3.15 g, 34.6 mmol) were dissolved in methanol (30 mL). To the solution was added hydrochloric acid (0.1 mL) and the mixture was vigorously stirred at room temperature for 15 hours. To the reaction mixture was added water (30 mL), and the deposited crystals were collected by filtration. The collected crystals were washed with water and diisopropyl ether, and then dried to obtain acetophenone=thiosemicarbazone (5.64 g, 88%).

¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.30 (s, 3H), 7.37-7.40 (m, 3H), 7.91-7.94 (m, 3H), 8.27 (br s, 1H), 10.21 (br s, 1H)

Step 2: Acetophenone=thiosemicarbazone (300 mg, 0.889 mmol) obtained above was dissolved in acetic anhydride (1.0 mL, 11 mmol). After being refluxing under heating, the solution was cooled to room temperature with vigorous stirring. To the reaction mixture was added diisopropyl ether (3 mL), and the deposited crystals were collected by filtration. After the collected crystals were suspended in diisopropyl ether and stirred for 3 hours, the crystals were collected by filtration and dried to obtain Compound 1 (195 mg, 72%).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.01 (s, 3H), 2.19 (s, 3H), 2.28 (s, 3H), 7.24-7.36 (br s, 5H), 11.83 (br s, 1H)

Example 2 (Compound 2)

[0056]

Step 1: In a manner similar to that in Step 1 of Example 1, propiophenone=thiosemicarbazone (759 mg, 88%) was obtained from propiophenone (541 mg, 3.92 mmol) and thiosemicarbazide (382 mg, 4.18 mmol).

¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 1.01 (t, J = 7.4 Hz, 3H), 2.85 (br q, J = 7.4 Hz, 2H), 7.39 (m, 3H), 7.89 (m, 3H), 8.24 (br s, 1H), 10.30 (br s, 1H)

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 2 (601 mg, 76%) was obtained from propiophenone=thiosemicarbazone (559 mg, 2.70 mmol) obtained above.

¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 1.02 (t, J = 7.1 Hz, 3H), 2.00 (s, 3H), 2.21 (s, 3H), 2.38 (dt, J = 7.1, 7.3 Hz, 1H), 2.85 (dt, J = 7.1, 7.3 Hz, 1H), 7.23-7.38 (m, 5H), 11.59 (br s, 1H)

Example 3 (Compound 3)

[0057]

Step 1: In a manner similar to that in Step 1 of Example 1, n-butyl(phenyl)methanone=thiosemicarbazone (589 mg, 63%) was obtained from n-butyl(phenyl)methanone (649 mg, 4.00 mmol) and thiosemicarbazide (367 mg, 4.03 mmol).

¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 0.99 (t, J = 7.3 Hz, 3H), 1.38-1.49 (m, 4H), 2.96-2.99 (m, 2H), 7.37-7.39 (m, 3H), 7.87-7.91 (m, 3H), 8.26 (br s, 1H), 10.36 (br s, 1H)

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 3 (168 mg, 62%) was obtained from n-butyl(phenyl)methanone=thiosemicarbazone (200 mg, 0.850 mmol) obtained above.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 0.96 (t, J = 7.3 Hz, 3H), 1.25-1.34 (m, 1H), 1.36-1.54 (m, 2H), 1.68-1.80 (m, 1H), 2.18 (s, 3H), 2.20-2.26 (m, 1H), 2.26 (s, 3H), 2.99-3.10 (m, 1H), 7.22-7.40 (m, 5H), 8.22 (br s, 1H)

Example 4 (Compound 4)

[0058]

Step 1: In a manner similar to that in Step 1 of Example 1, isopropyl(phenyl)methanone=thiosemicarbazone (613 mg, 68%) was obtained from isopropyl(phenyl)methanone (608 mg, 4.10 mmol) and thiosemicarbazide (364 mg, 3.99 mmol).

¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 1.07 (d, J = 6.9 Hz, 6H), 2.82 (m, 1H), 7.28 (br d, J = 6.3 Hz, 2H), 7.51-7.60 (m, 3H), 7.78 (br s, 1H), 8.23 (br s, 1H), 8.43 (br s, 1H)

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 4 (217 mg, 52%) was obtained from isopropyl(phenyl)methanone=thiosemicarbazone (300 mg, 1.36 mmol) obtained above.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.04 (d, J = 6.9 Hz, 3H), 1.13 (d, J = 6.9 Hz, 3H), 2.09 (s, 3H), 2.19 (s, 3H), 3.86 (m, 1H), 7.25-7.36 (m, 3H), 7.75 (br d, J = 7.3 Hz, 2H), 8.08 (br s, 1H)

Example 5 (Compound 5)

[0059] In a manner similar to that in Step 1 and 2 of Example 1, Compound 5 (130 mg, 10%) was obtained from cyclopropyl(phenyl)methanone (649 mg, 4.00 mmol) and thiosemicarbazide (367 mg, 4.03 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 0.60-0.98 (m, 4H), 1.84 (s, 3H), 2.34 (s, 3H), 2.45 (m, 1H), 7.20-7.35 (m, 3H), 7.54 (br d, J = 8.7 Hz, 2H), 9.40 (br s, 1H)

Example 6 (Compound 6)

[0060] In a manner similar to that in Step 1 and 2 of Example 1, Compound 6 (150 mg, 29%) was obtained from benzophenone (0.20 g, 2.19 mmol) and thiosemicarbazide (400 mg, 2.20 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.89 (s, 3H), 2.32 (s, 3H), 7.25-7.52 (m, 10H), 9.13 (br s, 1H)

Example 7 (Compound 7)

[0061]

Step 1: In a manner similar to that in Step 1 of Example 1, acetophenone=4-methylthiosemicarbazone (1.51 g, 77%) was obtained from 4-methylthiosemicarbazide (1.00 g, 9.51 mmol) and acetophenone (1.33 mL, 11.4 mmol).

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 7 (1.03 g, 47%) was obtained from acetophenone=4-methylthiosemicarbazone (1.00 g, 9.51 mmol) obtained above.

¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.21 (s, 3H), 2.23 (s, 3H), 2.26 (s, 3H), 3.41 (s, 3H), 7.28-7.36 (m, 5H)

Example 8 (Compounds 8 and 9)

[0062] To a solution of 60% sodium hydride (110 mg, 2.70 mmol) in N,N-dimethylformamide (10.0 mL) was added Compound 1 (50.0 mg, 1.80 mmol) prepared in Example 1, and the mixture was stirred at room temperature for 30 minutes. To the reaction mixture was added ethyl iodide (0.22 mL, 2.70 mmol) and the reaction mixture was further stirred at room temperature for 12 hours. To the reaction mixture was added 5% aqueous ammonium chloride and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/1) to obtain Compound 8 (120 mg, 22%) and Compound 9 (330 mg, 60%).

Compound 8

[0063] ¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.19 (t, J = 7.0 Hz, 6H), 2.23 (s, 3H), 2.41 (s, 3H), 3.26 (q, J = 7.0 Hz, 4H), 7.21-7.45 (m, 5H)

Compound 9

[0064] ¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.36 (t, J = 7.2 Hz, 3H), 2.24 (s, 6H), 2.37 (s, 3H), 3.91 (q, J = 7.2 Hz, 2H), 7.22-7.41 (m, 5H)

Example 9 (Compounds 10 and 11)

[0065] In a manner similar to that in Example 8, Compound 10 (0.15 g, 26%) and compound 11 (0.27 g, 48%) were obtained from Compound 1 (0.50 g, 1.80 mmol) prepared in Example 1 and n-propyl iodide (0.26 mL, 2.70 mmol).

Compound 10

[0066] ¹H NMR (270 MHz, CDCl₃) δ (ppm): 0.89 (t, J = 7.6 Hz, 6H), 1.61 (br q, J = 7.6 Hz, 4H), 2.27 (s, 3H), 2.40 (s, 3H), 3.14 (br t, J = 7.3 Hz, 4H), 7.21-7.47 (m, 5H)

Compound 11

[0067] ¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.00 (t, J = 7.3 Hz, 3H), 1.74-1.82 (m, 2H), 2.28 (s, 6H), 2.36 (s, 3H), 3.75-3.86 (m, 2H), 7.21-7.44 (m, 5H)

Example 10 (Compounds 12 and 13)

[0068] In a manner similar to that in Example 8, Compound 12 (120 mg, 16%) and Compound 13 (0.22 g, 33%) were obtained from Compound 1 (500 mg, 1.80 mmol) prepared in Example 1 and benzyl bromide (0.32 mL, 2.70 mmol).

Compound 12

[0069] ¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.24 (s, 3H), 2.46 (s, 3H), 4.43 (s, 4H), 7.14-7.49 (m, 15H)

Compound 13

[0070] ¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.16 (s, 3H), 2.26 (s, 3H), 2.36 (s, 3H), 5.11 (br s, 2H), 7.22-7.38 (m, 10H)

Example 11 (Compound 14)

[0071] To acetophenone=thiosemicarbazone (10.0 g, 51.8 mmol) prepared in Step 1 of Example 1 was added acetic anhydride (4.90 mL, 51.9 mmol) and pyridine (8.40 mL, 104 mmol), and the mixture was stirred at room temperature for 12 hours. After the reaction mixture was concentrated under reduced pressure, ethyl acetate and 2 mol/L aqueous sodium hydroxide was added, and the mixture was subjected to separation. The organic layer was washed with saturated aqueous ammonium chloride and saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate, and then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/1) to obtain Compound 14 (9.22 g, 76%).

¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.12 (s, 3H), 2.31 (s, 3H), 6.49 (br s, 2H), 7.21-7.41 (m, 5H)

Example 12 (Compound 15)

[0072] Compound 7 (550 mg, 1.89 mmol) prepared in Example 7 was dissolved in N,N-dimethylformamide (10.0 mL). To the solution was added 60% sodium hydride (0.23 g, 5.75 mmol) and the mixture was stirred at room temperature for 30 minutes. To the reaction mixture was added water and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous ammonium chloride and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/1) to obtain Compound 15 (0.31 g, 66%).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.17 (s, 3H), 2.41 (s, 3H), 2.91 (br d, J = 5.0 Hz, 3H), 3.92 (br s, 1H), 7.25-7.47 (m, 5H)

Example 13 (Compound 16)

[0073] To a solution of 60% sodium hydride (50.0 mg, 1.20 mmol) in N,N-dimethylformamide (2.0 mL) was added Compound 14 (100 mg, 0.41 mmol) prepared in Example 11, and the mixture was stirred at room temperature for 30 minutes. To the reaction mixture was added methyl iodide (0.08 mL, 1.24 mmol), and the mixture was further stirred at room temperature for 12 hours. To the reaction mixture was added 5% aqueous ammonium chloride and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/1) to obtain Compound 16 (70.0 mg, 67%). ¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.26 (s, 3H), 2.41 (s, 3H), 2.91 (s, 6H), 7.23-7.48 (m, 5H)

Example 14 (Compound 17)

[0074] In a manner similar to that in Example 12, Compound 17 (580 mg, 71%) was obtained from Compound 19 (1.00 g, 3.13 mmol) obtained in the after-mentioned.

Example 16.

[0075] ¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.13 (t, J = 7.2 Hz, 3H), 2.39 (s, 3H), 2.61 (q, J = 7.2 Hz, 2H), 2.88 (d, J = 6.3 Hz, 3H), 4.02 (br d, J = 6.3 Hz, 1H), 7.22-7.38 (m, 5H)

Example 15 (Compound 18)

[0076] Compound 17 (100 mg, 0.38 mmol) prepared in Example 14 was dissolved in acetone (2.0 mL). To the solution was added acetyl chloride (0.15 mL, 2.11 mmol) and pyridine (0.15 mL, 1.85 mmol), and the mixture was stirred at room temperature for 2 hours. To the reaction mixture was added ethyl acetate and 2 mol/L aqueous sodium hydroxide, and the solution was subjected to separation. The organic layer was washed with saturated aqueous ammonium chloride and saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate, and then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/2) to obtain Compound 18 (0.07 g, 59%). ¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.12 (t, J = 7.6 Hz, 3H), 2.27 (s, 3H), 2.35 (s, 3H), 2.65 (q, J = 7.6 Hz, 2H), 3.45 (s, 3H), 7.23-7.42 (m, 5H)

Example 16 (Compound 19)

[0077] To acetophenone=4-methylthiosemicarbazone (2.00 g, 9.66 mmol) prepared in Step 1 of Example 7 was added propionic anhydride (8.67 mL, 87.6 mmol), and the mixture was heated and stirred at 100°C for 3 hours. To the

reaction mixture was added ethyl acetate and 2 mol/L aqueous sodium hydroxide. After the mixture was stirred at room temperature for 30 minutes, the mixture was subjected to separation. The organic layer was washed with saturated aqueous ammonium chloride and saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate, and then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography

(ethyl acetate/n-hexane = 1/2) to obtain Compound 19 (1.39 g, 45%).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.12 (t, J = 7.3 Hz, 3H), 1.17 (t, J = 7.5 Hz, 3H), 2.36 (s, 3H), 2.54 (q, J = 7.3 Hz, 2H), 2.66 (q, J = 7.5 Hz, 2H), 3.45 (s, 3H), 7.21-7.42 (m, 5H)

Example 17 (Compound 20)

[0078] In a manner similar to that in Example 16, Compound 20 (1.55 g, 46%) was obtained from acetophenone=4-methylthiosemicarbazone (2.00 g, 9.66 mmol) prepared in Step 1 of Example 7 and butyric anhydride (11.1 mL, 67.8 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 0.95 (t, J = 7.3 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H), 1.15-1.78 (m, 4H), 2.35 (s, 3H), 2.49 (t, J = 7.3 Hz, 2H), 2.61 (t, J = 7.4 Hz, 2H), 3.45 (s, 3H), 7.21-7.42 (m, 5H)

Example 18 (Compound 21)

[0079] In a manner similar to that in Example 16, Compound 21 (1.43 g, 43%) was obtained from acetophenone=4-methylthiosemicarbazone (2.00 g, 9.66 mmol) prepared in Step 1 of Example 7 and isobutyric anhydride (11.2 mL, 67.5 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.05-1.25 (m, 12H), 2.34 (s, 3H), 2.99 (q, J = 7.3 Hz, 1H), 3.25 (q, J = 7.5 Hz, 1H), 3.50 (s, 3H), 7.21-7.45 (m, 5H)

Example 19 (Compound 22)

[0080]

Step 1: In a manner similar to that in Step 1 of Example 1, acetone=thiosemicarbazone (215 mg, 41%) was obtained from acetone (4.8 g, 40 mmol) and thiosemicarbazide (364 mg, 3.99 mmol).

¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 1.89 (s, 3H), 1.91 (s, 3H), 7.51 (br s, 1H), 7.98 (br s, 1H), 9.90 (br s, 1H)
Step 2: In a manner similar to that in Step 2 of Example 1, Compound 22 (151 mg, 61%) was obtained from acetone=thiosemicarbazone (150 mg, 1.14 mmol) prepared above.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.98 (s, 6H), 2.19 (s, 3H), 2.20 (s, 3H), 9.06 (br s, 1H)

Example 20 (Compound 23)

[0081]

Step 1: In a manner similar to that in Step 1 of Example 1, 2-hexanone=thiosemicarbazone (671 mg, 97%) was obtained from 2-hexanone (401 mg, 4.00 mmol) and thiosemicarbazide (364 mg, 3.99 mmol).

¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 0.88 (t, J = 6.9 Hz, 3H), 1.23-1.31 (m, 2H), 1.41-1.50 (m, 2H), 1.88 (s, 3H), 2.17-2.23 (m, 2H), 7.44 (br s, 1H), 8.02 (br s, 1H), 9.88 (br s, 1H)

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 23 (255 mg, 57%) was obtained from 2-hexanone=thiosemicarbazone (300 mg, 1.73 mmol) prepared above.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 0.90 (t, J = 6.9 Hz, 3H), 1.23-1.38 (m, 3H), 1.52-1.56 (m, 1H), 1.84-2.18 (m, 1H), 1.97 (s, 3H), 2.18 (s, 3H), 2.19 (s, 3H), 2.44-2.55 (m, 1H), 8.68 (br s, 1H)

Example 21 (Compound 24)

[0082]

Step 1: In a manner similar to that in Step 1 of Example 1, benzylacetone=thiosemicarbazone (788 mg, 89%) was obtained from benzylacetone (593 mg, 4.00 mmol) and thiosemicarbazide (367 mg, 4.03 mmol).

¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 1.92 (s, 3H), 2.52 (m, 2H), 2.84 (m, 2H), 7.14-7.30 (m, 5H), 7.43 (br s, 1H), 8.03 (br s, 1H), 9.94 (br s, 1H)

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 24 (382 mg, 92%) was obtained from

benzylacetone=thiosemicarbazone (300 mg, 1.36 mmol) prepared above.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.00 (s, 3H), 2.17 (s, 3H), 2.13 (dd, J = 2.3, 10.2 Hz, 1H), 2.19 (s, 3H), 2.59 (dd, J = 2.2, 10.2 Hz, 1H), 2.87 (br d, J = 12.2 Hz, 1H), 2.95 (br s, J = 11.8 Hz, 1H), 7.14-7.29 (m, 5H), 8.39 (br s, 1H)

5 Example 22 (Compound 25)

[0083]

10 Step 1: In a manner similar to that in Step 1 of Example 1, benzylideneacetone=thiosemicarbazone (730 mg, 80%) was obtained 1 from benzylideneacetone (610 mg, 4.17 mmol) and thiosemicarbazide (371 mg, 4.07 mmol). ¹H NMR (300 MHz, CDCl₃) δ (ppm): 2.13 (s, 3H), 6.89 (d, J = 16.8 Hz, 1H), 7.10 (d, J = 16.8 Hz, 1H), 7.27-7.41 (m, 3H), 7.43-7.56 (m, 2H), 7.78 (br s, 1H), 8.26 (br s, 1H), 10.27 (br s, 1H)

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 25 (195 mg, 72%) was obtained from benzylideneacetone=thiosemicarbazone (300 mg, 0.889 mmol) prepared above.

15 ¹H NMR (300 MHz, DMSO-d₆) δ (ppm): 2.13 (s, 3H), 2.15 (s, 3H), 2.23 (s, 3H), 6.62 (d, J = 12.2 Hz, 1H), 6.65 (d, J = 12.2 Hz, 1H), 7.20-7.39 (m, 5H), 8.57 (br s, 1H)

Example 23 (Compound 26)

20 [0084]

Step 1: In a manner similar to that in Step 1 of Example 1, 5-Nonanone=thiosemicarbazone (553 mg, 64%) was obtained from 5-nonanone (569 mg, 4.00 mmol) and thiosemicarbazide (364 mg, 3.99 mmol).

25 ¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 0.87 (t, J = 6.9 Hz, 6H), 1.20-1.53 (m, 8H), 2.17-2.22 (m, 2H), 2.31-2.37 (m, 2H), 7.40 (br s, 1H), 8.00 (br s, 1H), 10.03 (br s, 1H)

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 26 (245 mg, 59%) was obtained from 5-nonanone=thiosemicarbazone (300 mg, 1.39 mmol) prepared above.

30 ¹H NMR (270 MHz, CDCl₃) δ (ppm): 0.90 (t, J = 6.9 Hz, 6H), 1.18-1.37 (m, 6H), 1.55-1.63 (m, 2H), 1.77-1.88 (m, 2H), 2.18 (s, 3H), 2.19 (s, 3H), 2.45-2.56 (m, 2H), 8.90 (br s, 1H)

Example 24 (Compound 27)

[0085]

35 Step 1: In a manner similar to that in Step 1 of Example 1, α-tetralone=thiosemicarbazone (797 mg, 88%) was obtained from α-tetralone (804 mg, 4.13 mmol) and thiosemicarbazide (368 mg, 4.04 mmol).

¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 1.78-1.82 (m, 2H), 2.65-2.75 (m, 4H), 7.15-7.27 (m, 3H), 7.97 (br s, 1H), 8.20-8.40 (m, 2H), 10.10 (br s, 1H)

40 Step 2: In a manner similar to that in Step 2 of Example 1, Compound 27 (324 mg, 78%) was obtained from α-tetralone=thiosemicarbazone (300 mg, 1.37 mmol) prepared above.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.89 (s, 3H), 2.09-2.22 (m, 2H), 2.28 (s, 3H), 2.36-2.41 (m, 1H), 2.80-2.86 (m, 2H), 2.97-3.08 (m, 1H), 7.01 (br d, J = 8.6 Hz, 1H), 7.08-7.18 (m, 2H), 7.40 (br d, J = 7.3 Hz, 1H), 9.24 (br s, 1H)

Example 25 (Compound 28)

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[0086]

50 Step 1: In a manner similar to that in Step 1 of Example 1, β-tetralone=thiosemicarbazone (684 mg, 75%) was obtained from β-tetralone (607 mg, 4.15 mmol) and thiosemicarbazide (379 mg, 4.16 mmol).

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 28 (301 mg, 65%) was obtained from β-tetralone=thiosemicarbazone (334 mg, 1.53 mmol) prepared above.

¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.12 (s, 3H), 2.15-2.30 (m, 1H), 2.24 (s, 3H), 3.05-3.09 (m, 2H), 3.14 (br d, J = 15.8 Hz, 1H), 3.23-3.41 (m, 1H), 4.38 (br d, J = 15.8 Hz, 1H), 6.99-7.00 (m, 1H), 7.02-7.25 (m, 3H), 8.42 (br s, 1H)

55

Example 26 (Compound 29)

[0087]

- 5 Step 1: In a manner similar to that in Step 1 of Example 1, 1-indanone=thiosemicarbazone (1.54 g, 94%) was obtained from 1-indanone (1.06 g, 8.00 mmol) and thiosemicarbazide (740 mg, 8.12 mmol).
¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.85-2.89 (m, 2H), 3.03-3.08 (m, 2H), 7.28-7.38 (m, 3H), 7.87 (br d, J = 7.6 Hz, 1H), 7.92 (br s, 1H), 8.17 (br s, 1H), 10.2 (br s, 1H)
- 10 Step 2: In a manner similar to that in Step 2 of Example 1, Compound 29 (184 mg, 44%) was obtained from 1-indanone=thiosemicarbazone (300 mg, 1.46 mmol) prepared above.
¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.17 (s, 3H), 2.24 (s, 3H), 2.58-2.65 (m, 1H), 2.96-3.07 (m, 1H), 3.13-3.21 (m, 2H), 7.15-7.27 (m, 3H), 7.32-7.37 (m, 1H), 9.60 (br s, 1H)

Example 27 (Compound 30)

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[0088]

- Step 1: In a manner similar to that in Step 1 of Example 1, cyclohexanone=thiosemicarbazone (479 mg, 70%) was obtained from cyclohexanone (393 mg, 4.00 mmol) and thiosemicarbazide (384 mg, 3.99 mmol).
- 20 ¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 1.55 (br s, 6H), 2.19-2.23 (m, 2H), 2.38 (br s, 2H), 7.50 (br s, 1H), 7.93 (br s, 1H), 10.13 (br s, 1H)
- Step 2: In a manner similar to that in Step 2 of Example 1, Compound 30 (214 mg, 72%) was obtained from cyclohexanone=thiosemicarbazone (200 mg, 1.17 mmol) prepared above.
¹H NMR (300 MHz, CDCl₃) δ (ppm): 1.25-1.53 (m, 3H), 1.58-1.68 (m, 1H), 1.81-1.86 (m, 2H), 2.03-2.08 (m, 2H),
 25 2.16 (s, 3H), 2.17 (s, 3H), 2.90-3.01 (m, 2H), 7.95 (br s, 1H)

Example 28 (Compound 31)

- [0089] In a manner similar to that in Step 1 and 2 of Example 1, Compound 31 (214 mg, 20%) was obtained from 2-norbomanone (452 mg, 4.10 mmol) and thiosemicarbazide (377 mg, 4.14 mmol).
- 30 ¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.32-1.67 (m, 5H), 1.76-1.89 (m, 2H), 2.18 (s, 3H), 2.19 (br s, 1H), 2.21 (s, 3H), 2.26 (br s, 1H), 3.60 (br d, J = 13.9 Hz, 1H), 8.20 (br s, 1H)

Example 29 (Compound 32)

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- [0090] In a manner similar to that in Step 1 and 2 of Example 1, Compound 32 (214 mg, 32%) was obtained from 1'-acetonaphthone (344 mg, 2.02 mmol) and thiosemicarbazide (190 mg, 2.08 mmol).
- ¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.06 (s, 3H), 2.07 (s, 3H), 2.33 (s, 3H), 7.45-7.65 (m, 4H), 7.89-7.99 (m, 3H), 11.50 (br s, 1H)
- 40

Example 30 (Compound 33)

[0091]

- 45 Step 1: In a manner similar to that in Step 1 of Example 1, 2'-acetonaphthone=thiosemicarbazone (448 mg, 92%) was obtained from 2'-acetonaphthone (342 mg, 2.10 mmol) and thiosemicarbazide (189 mg, 2.07 mmol).
¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.42 (s, 3H), 7.53 (m, 2H), 7.86-8.05 (m, 4H), 8.28-8.34 (m, 3H), 10.28 (br s, 1H)
- Step 2: In a manner similar to that in Step 2 of Example 1, Compound 33 (302 mg, 90%) was obtained from 2'-acetonaphthone=thiosemicarbazone (250 mg, 1.03 mmol) prepared above.
- 50 ¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.02 (s, 3H), 2.22 (s, 3H), 2.38 (s, 3H), 7.51-7.55 (m, 3H), 7.85-7.95 (m, 4H), 11.68 (br s, 1H)

Example 31 (Compound 34)

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[0092]

Step 1: In a manner similar to that in Step 1 of Example 1, 1-(2-pyridyl)ethanone=thiosemicarbazone (694 mg,

88%) was obtained from 2-acetylpyridine (485 mg, 4.00 mmol) and thiosemicarbazide (369 mg, 4.05 mmol).

¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.38 (s, 3H), 7.37 (br t, J = 6.3 Hz, 1H), 7.78 (br t, J = 7.2 Hz, 1H), 8.13 (br s, 1H), 8.40 (br s, 1H), 8.41 (br d, J = 8.2 Hz, 1H), 8.56 (br d, J = 6.6 Hz, 1H), 10.31 (br s, 1H)

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 34 (160 mg, 37%) was obtained from 1-(2-pyridyl)ethanone=thiosemicarbazone (304 mg, 1.56 mmol) prepared above.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.09 (s, 3H), 2.26 (s, 3H), 2.42 (s, 3H), 7.17 (br t, J = 6.9 Hz, 1H), 7.38 (br d, J = 8.2 Hz, 1H), 7.68 (br t, J = 7.7 Hz, 1H), 8.44 (br s, 1H), 8.58 (br d, J = 6.3 Hz, 1H)

Example 32 (Compound 35)

[0093]

Step 1: In a manner similar to that in Step 1 of Example 1, 1-(3-pyridyl)ethanone=thiosemicarbazone (722 mg, 93%) was obtained from 3-acetylpyridine (484 mg, 4.00 mmol) and thiosemicarbazide (388 mg, 4.00 mmol).

¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.32 (s, 3H), 7.32-7.42 (m, 1H), 8.07 (br s, 1H), 8.29-8.34 (m, 2H), 8.54-8.57 (m, 1H), 9.09 (br s, 1H), 10.32 (br s, 1H)

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 35 (213 mg, 72%) was obtained from 1-(3-pyridyl)ethanone=thiosemicarbazone (205 mg, 1.05 mmol) prepared above.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.14 (s, 3H), 2.21 (s, 3H), 2.39 (s, 3H), 7.31 (br dd, J = 5.4, 7.9 Hz, 1H), 7.75 (br d, J = 7.9 Hz, 1H), 8.52 (br d, J = 5.4 Hz, 1H), 8.72 (br s, 1H), 9.08 (br s, 1H)

Example 33 (Compound 36)

[0094]

Step 1: In a manner similar to that in Step 1 of Example 1, 1-(4-pyridyl)ethanone=thiosemicarbazone (722 mg, 95%) was obtained from 4-acetylpyridine (507 mg, 4.19 mmol) and thiosemicarbazide (408 mg, 4.46 mmol).

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 36 (389 mg, 85%) was obtained from 1-(4-pyridyl)ethanone=thiosemicarbazone (318 mg, 1.64 mmol) prepared above.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.16 (s, 3H), 2.25 (s, 3H), 2.35 (s, 3H), 7.30 (d, J = 6.3 Hz, 2H), 8.46 (br s, 1H), 8.60 (d, J = 6.3 Hz, 2H)

Example 34 (Compound 37)

[0095]

Step 1: In a manner similar to that in Step 1 of Example 1, 1-pyrazinylethanone=thiosemicarbazone (714 mg, 92%) was obtained from acetylpyrazine (489 mg, 4.00 mmol) and thiosemicarbazide (366 mg, 4.00 mmol).

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 37 (489 mg, 85%) was obtained from 1-pyrazinylethanone=thiosemicarbazone (400 mg, 2.05 mmol) prepared above.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.16 (s, 3H), 2.26 (s, 3H), 2.42 (s, 3H), 8.06 (br s, 1H), 8.46 (d, J = 2.7 Hz, 1H), 8.52 (dd, J = 1.7, 2.7 Hz, 1H), 8.71 (d, J = 1.7 Hz, 1H)

Example 35 (Compound 38)

[0096]

Step 1: In a manner similar to that in Step 1 of Example 1, 1-(2-pyrrolyl)ethanone=thiosemicarbazone (408 mg, 55%) was obtained from 2-acetylpyrrole (437 mg, 4.00 mmol) and thiosemicarbazide (374 mg, 4.09 mmol).

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 38 (504 mg, 95%) was obtained from 1-(2-pyrrolyl)ethanone=thiosemicarbazone (314 mg, 1.72 mmol) prepared above.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.12 (s, 3H), 2.21 (s, 3H), 2.38 (s, 3H), 2.55 (s, 3H), 6.17-6.22 (m, 2H), 7.11 (br s, 1H), 8.13 (br s, 1H)

Example 36 (Compound 39)

[0097]

Step 1: In a manner similar to that in Step 1 of Example 1, 1-(2-furyl)ethanone=thiosemicarbazone (441 mg, 60%) was obtained from 2-acetylfuran (444 mg, 4.00 mmol) and thiosemicarbazide (368 mg, 4.03 mmol).

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 39 (217 mg, 83%) was obtained from 1-(2-furyl)ethanone=thiosemicarbazone (180 mg, 0.982 mmol) prepared above.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.13 (s, 3H), 2.22 (s, 3H), 2.30 (s, 3H), 6.31 (m, 2H), 7.36 (br s, 1H), 8.43 (br s, 1H)

Example 37 (Compound 40)

[0098]

Step 1: In a manner similar to that in Step 1 of Example 1, 1-(2-thienyl)ethanone=thiosemicarbazone (636 mg, 78%) was obtained from 2-acetylthiophene (521 mg, 4.13 mmol) and thiosemicarbazide (376 mg, 4.11 mmol).

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 40 (549 mg, 78%) was obtained from 1-(2-thienyl)ethanone=thiosemicarbazone (498 mg, 2.50 mmol) prepared above.

¹H NMR (300 MHz, CDCl₃) δ (ppm): 2.07 (s, 3H), 2.24 (s, 3H), 2.42 (s, 3H), 6.89 (br t, J = 7.2 Hz, 1H), 7.06 (dd, J = 6.9, 7.2 Hz, 1H), 7.24 (br d, J = 6.9 Hz, 1H), 8.81 (br s, 1H)

Example 38 (Compound 41)

In a manner similar to that in Example 8, Compound 41 (148 mg, 52%) was obtained in from Compound 40 (260 mg, 0.918 mmol) prepared in Example 37.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.36 (t, J = 7.0 Hz, 3H), 2.25 (s, 3H), 2.30 (s, 3H), 2.43 (s, 3H), 3.92 (br q, J = 7.0 Hz, 2H), 6.91 (br t, J = 5.2 Hz, 1H), 7.06 (br d, J = 5.2 Hz, 1H), 7.24 (br d, J = 5.2 Hz, 1H)

Example 39 (Compound 42)

[0100]

Step 1: In a manner similar to that in Step 1 of Example 1, 1-(3-methyl-2-thienyl)ethanone=thiosemicarbazone (410 mg, 48%) was obtained from 2-acetyl-3-methylthiophene (561 mg, 4.00 mmol) and thiosemicarbazide (374 mg, 4.09 mmol).

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 42 (335 mg, 93%) was obtained from 1-(3-methyl-2-thienyl)ethanone=thiosemicarbazone (260 mg, 1.22 mmol) prepared above.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.02 (s, 3H), 2.19 (s, 3H), 2.24 (s, 3H), 2.38 (s, 3H), 6.78 (d, J = 5.0 Hz, 1H), 7.07 (d, J = 5.0 Hz, 1H), 9.37 (br s, 1H)

Example 40 (Compound 43)

[0101]

Step 1: In a manner similar to that in Step 1 of Example 1, 1-(benzo[b]thiophen-2-yl)ethanone=thiosemicarbazone (990 mg, 99%) was obtained from 1-(benzo[b]thiophen-2-yl)ethanone (705 mg, 4.00 mmol) and thiosemicarbazide (370 mg, 4.05 mmol).

¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.40 (s, 3H), 7.36-7.41 (m, 2H), 7.45 (br s, 1H), 7.81-7.90 (m, 3H), 8.42 (br s, 1H), 10.58 (br s, 1H)

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 43 (599 mg, 90%) was obtained from 1-(benzo[b]thiophen-2-yl)ethanone=thiosemicarbazone (500 mg, 2.01 mmol) prepared above.

¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.04 (s, 3H), 2.17 (s, 3H), 2.38 (s, 3H), 7.31-7.40 (m, 3H), 7.79 (br d, J = 7.6 Hz, 1H), 7.89 (br d, J = 7.8 Hz, 1H), 11.75 (br s, 1H)

Example 41 (Compound 44)

[0102]

- 5 Step 1: In a manner similar to that in Step 1 of Example 1, 1-(3-thienyl)ethanone=thiosemicarbazone (839 mg, 98%) was obtained from 3-acetylthiophene (520 mg, 4.12 mmol) and thiosemicarbazide (366 mg, 4.00 mmol).
¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.27 (s, 3H), 7.52 (br d, J = 5.3 Hz, 1H), 7.83 (br d, J = 5.3 Hz, 1H), 7.95 (br s, 1H), 8.22 (br s, 1H), 10.08 (br s, 1H)
- 10 Step 2: In a manner similar to that in Step 2 of Example 1, Compound 44 (540 mg, 83%) was obtained from 1-(3-thienyl)ethanone=thiosemicarbazone (458 mg, 2.30 mmol) prepared above.
¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.02 (s, 3H), 2.15 (s, 3H), 2.25 (s, 3H), 7.05 (br d, J = 6.0 Hz, 1H), 7.37 (br s, 1H), 7.47 (br d, J = 6.0 Hz, 1H)

Example 42 (Compound 45)

15

[0103]

- 20 Step 1: In a manner similar to that in Step 1 of Example 1, 1-(2-thiazolyl)ethanone=thiosemicarbazone (711 mg, 90%) was obtained from 2-acetylthiazole (379 mg, 4.15 mmol) and thiosemicarbazide (366 mg, 4.00 mmol).
¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.42 (s, 3H), 7.67 (br s, 1H), 7.79 (br d, J = 4.3 Hz, 1H), 7.87 (br d, J = 4.3 Hz, 1H), 8.51 (br s, 1H), 10.65 (br s, 1H)
- Step 2: In a manner similar to that in Step 2 of Example 1, Compound 45 (374 mg, 45%) was obtained from 1-(2-thiazolyl)ethanone=thiosemicarbazone (374 mg, 1.87 mmol) prepared above.
¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.03 (s, 3H), 2.18 (s, 3H), 2.31 (s, 3H), 7.74-7.79 (m, 2H), 11.70 (br s, 1H)

25

Example 43 (Compound 46)

- [0104] In a manner similar to that in Step 1 and 2 of Example 1, Compound 46 (141 mg, 10%) was obtained from 2'-methylacetophenone (627 mg, 4.67 mmol) and thiosemicarbazide (374 mg, 4.09 mmol).
 30 ¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.99 (br s, 1H), 2.21 (s, 3H), 2.33 (s, 3H), 2.38 (s, 3H), 7.15-7.20 (m, 3H), 7.38 (m, 1H), 8.90 (br s, 1H)

Example 44 (Compound 47)

35

[0105]

- Step 1: In a manner similar to that in Step 1 of Example 1, 3'-methylacetophenone=thiosemicarbazone (791 mg, 89%) was obtained from 3'-methylacetophenone (540 mg, 4.02 mmol) and thiosemicarbazide (369 mg, 4.04 mmol).
 40 Step 2: In a manner similar to that in Step 2 of Example 1, Compound 47 (316 mg, 79%) was obtained from 3'-methylacetophenone=thiosemicarbazone (300 mg, 1.36 mmol) prepared above.
¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.15 (s, 3H), 2.23 (s, 3H), 2.34 (s, 3H), 2.37 (s, 3H), 7.01-7.09 (m, 1H), 7.19-7.30 (m, 3H), 7.90 (br s, 1H)

Example 45 (Compound 48)

45

[0106]

- 50 Step 1: In a manner similar to that in Step 1 of Example 1, 4'-methylacetophenone=thiosemicarbazone (767 mg, 93%) was obtained from 4'-methylacetophenone (536 mg, 3.99 mmol) and thiosemicarbazide (382 mg, 4.19 mmol).
¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.27 (s, 3H), 2.32 (s, 3H), 7.18 (d, J = 7.9 Hz, 2H), 7.82 (d, J = 7.9 Hz, 2H), 7.88 (br s, 1H), 8.23 (br s, 1H), 10.15 (br s, 1H)
- Step 2: In a manner similar to that in Step 2 of Example 1, Compound 48 (224 mg, 80%) was obtained from 4'-methylacetophenone=thiosemicarbazone (200 mg, 0.965 mmol) prepared above.
¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.06 (s, 3H), 2.24 (s, 3H), 2.31 (s, 3H), 2.36 (s, 3H), 7.13 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 8.40 (br s, 1H)

55

Example 46 (Compound 49)

[0107]

- 5 Step 1: In a manner similar to that in Step 1 of Example 1, 2'-ethylpropiophenone=thiosemicarbazone (672 mg, 71%) was obtained from 2'-ethylpropiophenone (649 mg, 4.00 mmol) and thiosemicarbazide (378 mg, 4.14 mmol).
 Step 2: In a manner similar to that in Step 2 of Example 1, Compound 49 (759 mg, 88%) was obtained from 2'-ethylpropiophenone=thiosemicarbazone (300 mg, 1.27 mmol) prepared above.
¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.13 (t, J = 6.9 Hz, 3H), 1.24 (t, J = 7.3 Hz, 3H), 1.96 (s, 3H), 2.20 (m, 1H),
 10 2.24 (s, 3H), 2.71 (m, 2H), 3.14 (m, 1H), 7.13 (br t, J = 7.1 Hz, 1H), 7.21-7.26 (m, 2H), 7.51 (br d, J = 7.9 Hz, 1H),
 8.87 (br s, 1H)

Example 47 (Compound 50)

15 [0108]

- Step 1: In a manner similar to that in Step 1 of Example 1, 2'-methoxyacetophenone=thiosemicarbazone (891 mg, 92%) was obtained from 2'-methoxyacetophenone (601 mg, 4.00 mmol) and thiosemicarbazide (366 mg, 4.00 mmol).
 20 Step 2: In a manner similar to that in Step 2 of Example 1, Compound 50 (64.0 mg, 93%) was obtained from 2'-methoxyacetophenone=thiosemicarbazone (50.0 mg, 0.224 mmol) prepared above.
¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.08 (s, 3H), 2.29 (s, 3H), 2.45 (s, 3H), 3.87 (s, 3H), 6.90 (br t, J = 7.3 Hz, 1H), 6.91 (br d, J = 7.3 Hz, 1H), 7.06 (br d, J = 7.3 Hz, 1H), 7.27 (br t, J = 7.3 Hz, 1H), 8.31 (br s, 1H)

25 Example 48 (Compound 51)

[0109]

- 30 Step 1: In a manner similar to that in Step 1 of Example 1, 3'-methoxyacetophenone=thiosemicarbazone (713 mg, 58%) was obtained from 3'-methoxyacetophenone (601 mg, 4.00 mmol) and thiosemicarbazide (377 mg, 4.12 mmol).
¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.29 (s, 3H), 3.80 (s, 3H), 6.96 (br d, J = 7.9 Hz, 1H), 7.30 (br t, J = 7.9 Hz, 1H), 7.44 (br s, 1H), 7.46 (br d, J = 7.9 Hz, 1H), 7.94 (br s, 1H), 8.28 (br s, 1H), 10.18 (br s, 1H)
 Step 2: In a manner similar to that in Step 2 of Example 1, Compound 51 (419 mg, 71%) was obtained from 3'-methoxyacetophenone=thiosemicarbazone (500 mg, 2.24 mmol) prepared above.
 35 ¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.10 (s, 3H), 2.30 (s, 3H), 2.34 (s, 3H), 3.78 (s, 3H), 6.78 (br d, J = 7.9 Hz, 1H), 6.94 (br s, 1H), 7.01 (br d, J = 7.9 Hz, 1H), 7.25 (br t, J = 7.9 Hz, 1H), 9.48 (br s, 1H)

40 Example 49 (Compound 52)

[0110]

- 45 Step 1: In a manner similar to that in Step 1 of Example 1, 4'-methoxyacetophenone=thiosemicarbazone (448 mg, 83%) was obtained from 4'-methoxyacetophenone (362 mg, 2.41 mmol) and thiosemicarbazide (225 mg, 2.46 mmol).
 Step 2: In a manner similar to that in Step 2 of Example 1, Compound 52 (248 mg, 90%) was obtained from 4'-methoxyacetophenone=thiosemicarbazone (200 mg, 0.896 mmol) prepared above.
¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.06 (s, 3H), 2.24 (s, 3H), 2.35 (s, 3H), 3.78 (s, 3H), 6.84 (d, J = 8.6 Hz, 2H),
 50 7.36 (d, J = 8.6 Hz, 2H), 8.56 (br s, 1H)

Example 50 (Compound 53)

[0111]

- 55 Step 1: In a manner similar to that in Step 1 of Example 1, 2'-fluoroacetophenone=thiosemicarbazone (704 mg, 83%) was obtained from 2'-fluoroacetophenone (558 mg, 4.04 mmol) and thiosemicarbazide (385 mg, 4.12 mmol).
¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.29 (s, 3H), 7.19-7.28 (m, 2H), 7.40-7.48 (m, 1H), 7.74-7.80 (m, 2H), 8.30 (br s, 1H), 10.34 (br s, 1H)

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 53 (199 mg, 71%) was obtained from 2'-fluoroacetophenone=thiosemicarbazone (200 mg, 0.948 mmol) prepared above.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.05 (s, 3H), 2.26 (s, 3H), 2.40 (s, 3H), 7.01-7.12 (m, 2H), 7.23-7.31 (m, 2H), 8.68 (br s, 1H)

Example 51 (Compound 54)

[0112]

Step 1: In a manner similar to that in Step 1 of Example 1, 3'-fluoroacetophenone=thiosemicarbazone (772 mg, 92%) was obtained from 3'-fluoroacetophenone (553 mg, 4.00 mmol) and thiosemicarbazide (372 mg, 4.07 mmol).

¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.29 (s, 3H), 7.17-7.24 (m, 1H), 7.38-7.46 (m, 1H), 7.69 (br d, J = 8.9 Hz, 1H), 7.88 (br d, J = 11.2 Hz, 1H), 8.09 (br s, 1H), 8.31 (br s, 1H), 10.24 (br s, 1H)

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 54 (242 mg, 74%) was obtained from 3'-fluoroacetophenone=thiosemicarbazone (233 mg, 1.10 mmol) prepared above.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.08 (s, 3H), 2.26 (s, 3H), 2.35 (s, 3H), 6.92-6.99 (m, 1H), 7.07-7.13 (m, 1H), 7.18-7.22 (m, 1H), 7.28-7.34 (m, 1H), 8.54 (br s, 1H)

Example 52 (Compound 55)

[0113]

Step 1: In a manner similar to that in Step 1 of Example 1, 4'-fluoroacetophenone=thiosemicarbazone (769 mg, 91%) was obtained from 4'-fluoroacetophenone (553 mg, 4.00 mmol) and thiosemicarbazide (376 mg, 4.11 mmol).

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 55 (251 mg, 86%) was obtained from 4'-fluoroacetophenone=thiosemicarbazone (208 mg, 0.986 mmol) prepared above.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.14 (s, 3H), 2.22 (s, 3H), 2.36 (s, 3H), 6.98-7.05 (m, 2H), 7.38-7.44 (m, 2H), 8.09 (br s, 1H)

Example 53 (Compound 56)

[0114]

Step 1: In a manner similar to that in Step 1 of Example 1, 2'-chloroacetophenone=thiosemicarbazone (362 mg, 58%) was obtained from 2'-chloroacetophenone (344 mg, 2.23 mmol) and thiosemicarbazide (194 mg, 2.12 mmol).

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 56 (347 mg, 97%) was obtained from 2'-chloroacetophenone=thiosemicarbazone (200 mg, 1.14 mmol) prepared above.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.98 (s, 3H), 2.23 (s, 3H), 2.38 (s, 3H), 7.22-7.27 (m, 2H), 7.37-7.45 (m, 2H), 9.05 (br s, 1H)

Example 54 (Compound 57)

[0115] In a manner similar to that in Example 8, Compound 57 (347 mg, 97%) was obtained from Compound 56 (200 mg, 1.14 mmol) prepared in Example 53.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.35 (t, J = 8.9 Hz, 3H), 2.25 (s, 3H), 2.30 (s, 3H), 2.40 (s, 3H), 3.91-3.93 (br s, 2H), 7.22-7.28 (m, 2H), 7.38-7.42 (m, 2H)

Example 55 (Compound 58)

[0116]

Step 1: In a manner similar to that in Step 1 of Example 1, 3'-chloroacetophenone=thiosemicarbazone (211 mg, 45%) was obtained from 3'-chloroacetophenone (319 mg, 2.06 mmol) and thiosemicarbazide (188 mg, 2.06 mmol).

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 58 (347 mg, 97%) was obtained from 3'-chloroacetophenone=thiosemicarbazone (200 mg, 1.14 mmol) prepared above.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.01 (s, 3H), 2.19 (s, 3H), 2.25 (s, 3H), 7.29-7.41 (m, 4H), 11.68 (br s, 1H)

Example 56 (Compound 59)

[0117]

- 5 Step 1: In a manner similar to that in Step 1 of Example 1, 4'-chloroacetophenone=thiosemicarbazone (362 mg, 58%) was obtained from 4'-chloroacetophenone (344 mg, 2.23 mmol) and thiosemicarbazide (194 mg, 2.06 mmol).
 Step 2: In a manner similar to that in Step 2 of Example 1, Compound 59 (193 mg, 86%) was obtained from 4'-chloroacetophenone=thiosemicarbazone (164 mg, 0.720 mmol) prepared above.
¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.11 (s, 3H), 2.23 (s, 3H), 2.24 (s, 3H), 7.30 (d, J = 8.6 Hz, 2H), 7.36 (d, J = 8.6 Hz, 2H), 8.34 (br s, 1H)
- 10

Example 57 (Compound 60)

[0118]

- 15 Step 1: In a manner similar to that in Step 1 of Example 1, 2'-bromoacetophenone=thiosemicarbazone (392 mg, 69%) was obtained from 2'-bromoacetophenone (415 mg, 2.08 mmol) and thiosemicarbazide (190 mg, 2.08 mmol).
¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.28 (s, 3H), 7.29-7.76 (m, 5H), 8.25 (br s, 1H), 10.35 (br s, 1H)
 Step 2: In a manner similar to that in Step 2 of Example 1, Compound 60 (328 mg, 99%) was obtained from 2'-bromoacetophenone=thiosemicarbazone (254 mg, 0.933 mmol) prepared above.
¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.01 (s, 3H), 2.23 (s, 3H), 2.38 (s, 3H), 7.13 (br t, J = 7.6 Hz, 1H), 7.30 (br t, J = 7.6 Hz, 1H), 7.47 (br d, J = 7.6 Hz, 1H), 7.62 (br s, J = 7.6 Hz, 1H), 8.86 (br s, 1H)
- 20

Example 58 (Compound 61)

25

[0119]

- 30 Step 1: In a manner similar to that in Step 1 of Example 1, 2'-hydroxyacetophenone=thiosemicarbazone (649 mg, 78%) was obtained from 2'-hydroxyacetophenone (544 mg, 4.00 mmol) and thiosemicarbazide (377 mg, 4.12 mmol).
¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.31 (s, 3H), 6.85 (br t, J = 7.0 Hz, 1H), 6.88 (br d, J = 7.0 Hz, 1H), 7.25 (br t, J = 7.0 Hz, 1H), 7.50 (br s, 1H), 7.53 (br d, J = 7.0 Hz, 1H), 7.81 (br s, 1H), 8.10 (br s, 1H), 10.35 (br s, 1H)
 Step 2: In a manner similar to that in Step 2 of Example 1, Compound 61 (322 mg, 70%) was obtained from 2'-hydroxyacetophenone=thiosemicarbazone (233 mg, 1.10 mmol) prepared above.
¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.04 (s, 3H), 2.06 (s, 3H), 2.23 (s, 3H), 2.24 (s, 3H), 7.12 (br d, J = 7.6 Hz, 1H), 7.23 (br t, J = 7.6 Hz, 1H), 7.35 (br t, J = 7.6 Hz, 1H), 7.39 (br d, J = 7.6 Hz, 1H), 10.20 (br s, 1H)
- 35

Example 59 (Compound 62)

40

[0120]

- Step 1: In a manner similar to that in Step 1 of Example 1, 3'-hydroxyacetophenone=thiosemicarbazone (654 mg, 78%) was obtained from 3'-hydroxyacetophenone (546 mg, 4.01 mmol) and thiosemicarbazide (379 mg, 4.15 mmol).
 45 Step 2: In a manner similar to that in Step 2 of Example 1, Compound 62 (351 mg, 84%) was obtained from 3'-hydroxyacetophenone=thiosemicarbazone (262 mg, 1.25 mmol) prepared above.
¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 1.96 (s, 3H), 2.27 (s, 3H), 2.28 (s, 3H), 2.34 (s, 3H), 7.07 (br d, J = 8.4 Hz, 1H), 7.15 (br s, 1H), 7.32 (br d, J = 8.4 Hz, 1H), 7.33 (br t, J = 8.4 Hz, 1H), 9.24 (br s, 1H)

50 Example 60 (Compound 63)

[0121]

- 55 Step 1: In a manner similar to that in Step 1 of Example 1, 3'-hydroxybenzaldehyde=thiosemicarbazone (732 mg, 88%) was obtained from 3'-hydroxybenzaldehyde (488 mg, 4.00 mmol) and thiosemicarbazide (378 mg, 4.15 mmol).
¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 6.80 (m, 1H), 7.13 (br s, 1H), 7.19 (m, 2H), 7.87 (br s, 1H), 7.96 (s, 1H), 8.14 (br s, 1H), 9.56 (br s, 1H), 11.35 (br s, 1H)

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 63 (322 mg, 70%) was obtained from 3'-hydroxybenzaldehyde=thiosemicarbazone (300 mg, 1.43 mmol) prepared above.

¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.18 (s, 3H), 2.25 (s, 3H), 2.28 (s, 3H), 6.86 (s, 1H), 7.04 (br d, J = 7.4 Hz, 1H), 7.05 (s, 1H), 7.19 (br d, J = 7.4 Hz, 1H), 7.31 (br t, J = 7.4 Hz, 1H), 8.16 (br s, 1H)

Example 61 (Compound 64)

[0122]

Step 1: In a manner similar to that in Step 1 of Example 1, 4'-hydroxyacetophenone=thiosemicarbazone (830 mg, 99%) was obtained from 4'-hydroxyacetophenone (544 mg, 4.00 mmol) and thiosemicarbazide (387 mg, 4.25 mmol).

¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.23 (s, 3H), 6.75 (d, J = 8.5 Hz, 2H), 7.76 (d, J = 8.5 Hz, 2H), 7.78 (br s, 1H), 8.14 (br s, 1H), 9.75 (s, 1H), 10.05 (s, 1H)

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 64 (199 mg, 61%) was obtained from 4'-hydroxyacetophenone=thiosemicarbazone (202 mg, 0.965 mmol) prepared above.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.15 (s, 3H), 2.22 (s, 3H), 2.23 (s, 3H), 2.29 (s, 3H), 7.07 (br d, J = 8.6 Hz, 2H), 7.43 (br d, J = 8.6 Hz, 2H), 7.99 (br s, 1H)

Example 62 (Compound 65)

[0123]

Step 1: In a manner similar to that in Step 1 of Example 1, 2'-nitroacetophenone=thiosemicarbazone (785 mg, 81%) was obtained from 2'-nitroacetophenone (673 mg, 4.08 mmol) and thiosemicarbazide (365 mg, 3.99 mmol).

¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.27 (s, 3H), 7.32 (br s, 1H), 7.60-7.68 (m, 1H), 7.72-7.79 (m, 2H), 7.96 (br d, J = 7.9 Hz, 1H), 8.31 (br s, 1H), 10.52 (br s, 1H)

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 65 (548 mg, 94%) was obtained from 2'-nitroacetophenone=thiosemicarbazone (431 mg, 1.81 mmol) prepared above.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.04 (s, 3H), 2.07 (s, 3H), 2.23 (s, 3H), 7.49-7.71 (m, 4H), 11.73 (br s, 1H)

Example 63 (Compound 66)

[0124]

Step 1: In a manner similar to that in Step 1 of Example 1, 3'-nitroacetophenone=thiosemicarbazone (910 mg, 75%) was obtained from 3'-nitroacetophenone (661 mg, 4.00 mmol) and thiosemicarbazide (370 mg, 4.05 mmol).

¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.37 (s, 3H), 7.67 (br t, J = 7.9 Hz, 1H), 8.16 (br s, 1H), 8.23 (br d, J = 7.9 Hz, 1H), 8.40 (br s, 1H), 8.43 (br s, J = 7.9 Hz, 1H), 8.61 (br s, 1H), 10.40 (br s, 1H)

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 66 (409 mg, 60%) was obtained from 3'-nitroacetophenone=thiosemicarbazone (506 mg, 2.12 mmol) prepared above.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.15 (s, 3H), 2.25 (s, 3H), 2.40 (s, 3H), 7.53 (br t, J = 8.3 Hz, 1H), 7.73 (br d, J = 8.3 Hz, 1H), 8.15 (br d, J = 8.3 Hz, 1H), 8.30 (br s, 2H)

Example 64 (Compound 67)

[0125]

Step 1: In a manner similar to that in Step 1 of Example 1, 4'-nitroacetophenone=thiosemicarbazone (475 mg, 94%) was obtained from 4'-nitroacetophenone (350 mg, 2.12 mmol) and thiosemicarbazide (195 mg, 2.13 mmol).

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 67 (216 mg, 40%) was obtained from 4'-nitroacetophenone=thiosemicarbazone (397 mg, 1.67 mmol) prepared above.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.15 (s, 3H), 2.24 (s, 3H), 2.38 (s, 3H), 7.59 (d, J = 8.6 Hz, 2H), 8.20 (d, J = 8.6 Hz, 2H), 8.30 (br s, 1H)

Example 65 (Compound 68)

[0126] Compound 61 (118 mg, 0.352 mmol) prepared in Example 58 was dissolved in methanol (5 mL), and to the

solution was added potassium carbonate (200 mg, 1.48 mmol) and the mixture was stirred at room temperature for 10 minutes. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. After the residue was dissolved in ethyl acetate, to the solution was added water and 1 mol/L hydrochloric acid, and the mixture was subjected to separation. The organic layer was washed with saturated aqueous sodium chloride and dried over anhydrous sodium sulfate, and then the solvent was evaporated under reduced pressure. The resulting yellow oil was dissolved in methanol (3 mL). To the solution was added diisopropyl ether (10 mL), and the deposited crystals were collected by filtration and dried to obtain Compound 68 (96.9 mg, 94%).

¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 1.98 (s, 3H), 2.23 (s, 3H), 2.35 (s, 3H), 6.72 (br t, J = 7.6 Hz, 1H), 6.83 (br d, J = 7.6 Hz, 1H), 6.88 (br d, J = 7.6 Hz, 1H), 7.10 (br t, J = 7.6 Hz, 1H), 9.95 (br s, 1H), 11.45 (br s, 1H)

Example 66 (Compound 69)

[0127] In a manner similar to that in Example 65, Compound 69 (101 mg, 82%) was obtained from Compound 62 (140 mg, 0.417 mmol) prepared in Example 59.

¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.01 (s, 3H), 2.18 (s, 3H), 2.23 (s, 3H), 6.66 (br t, J = 7.9 Hz, 1H), 6.69 (br s, 1H), 6.76 (br d, J = 7.9 Hz, 1H), 7.13 (br t, J = 7.9 Hz, 1H), 9.46 (br s, 1H), 11.60 (br s, 1H)

Example 67 (Compound 70)

[0128] In a manner similar to that in Example 65, Compound 70 (88 mg, 91%) was obtained from Compound 64 (110 mg, 0.328 mmol) prepared in Example 61.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.00 (s, 3H), 2.16 (s, 3H), 2.23 (s, 3H), 6.71 (d, J = 8.6 Hz, 2H), 7.15 (d, J = 8.6 Hz, 2H), 9.48 (br s, 1H), 11.6 (br s, 1H)

Example 68 (Compound 71)

[0129]

Step 1: In a manner similar to that in Step 1 of Example 1, 3'-cyanoacetophenone=thiosemicarbazone (863 mg, 99%) was obtained from 3-acetylbenzonitrile (581 mg, 4.00 mmol) and thiosemicarbazide (370 mg, 4.05 mmol).

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 71 (274 mg, 68%) was obtained from 3'-cyanoacetophenone=thiosemicarbazone (300 mg, 1.34 mmol) prepared above.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.08 (s, 3H), 2.26 (s, 3H), 2.36 (s, 3H), 7.46 (m, 1H), 7.56 (m, 1H), 7.68 (m, 1H), 7.71 (br s, 1H), 8.73 (br s, 1H)

Example 69 (Compound 72)

[0130]

Step 1: In a manner similar to that in Step 1 of Example 1, 4'-cyanoacetophenone=thiosemicarbazone (430 mg, 98%) was obtained from 4-acetylbenzonitrile (290 mg, 2.0 mmol) and thiosemicarbazide (185 mg, 2.02 mmol).

¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.30 (s, 3H), 7.82 (d, J = 8.4 Hz, 2H), 8.12 (br s, 1H), 8.14 (d, J = 8.4 Hz, 2H), 8.40 (br s, 1H), 10.51 (br s, 1H)

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 72 (494 mg, 94%) was obtained from 4'-cyanoacetophenone=thiosemicarbazone (380 mg, 1.74 mmol) prepared above.

¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.01 (s, 3H), 2.18 (s, 3H), 2.31 (s, 3H), 7.54 (d, J = 11.7 Hz, 2H), 7.81 (d, J = 11.7 Hz, 2H), 11.73 (br s, 1H)

Example 70 (Compound 73)

[0131]

Step 1: In a manner similar to that in Step 1 of Example 1, 3'-trifluoromethylacetophenone=thiosemicarbazone (888 mg, 63%) was obtained from 3'-trifluoromethylacetophenone (765 mg, 4.07 mmol) and thiosemicarbazide (370 mg, 4.05 mmol).

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 73 (270 mg, 68%) was obtained from 3'-trifluoromethylacetophenone=thiosemicarbazone (300 mg, 1.15 mmol) prepared above.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.01 (s, 3H), 2.27 (s, 3H), 2.37 (s, 3H), 7.43 (br t, J = 7.6 Hz, 1H), 7.52 (br d,

J = 7.6 Hz, 1H), 7.63 (br d, J = 7.6 Hz, 1H), 7.65 (br s, 1H), 8.89 (br s, 1H)

Example 71 (Compound 74)

5 [0132]

Step 1: In a manner similar to that in Step 1 of Example 1, 2'-carboxyacetophenone=thiosemicarbazone (489 mg, 52%) was obtained from 2-acetylbenzoic acid (381 mg, 4.17 mmol) and thiosemicarbazide (381 mg, 4.17 mmol).

10 Step 2: In a manner similar to that in Step 2 of Example 1, Compound 74 (313 mg, 64%) was obtained from 2'-carboxyacetophenone=thiosemicarbazone (363 mg, 1.53 mmol) prepared above.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.04 (s, 3H), 2.29 (s, 3H), 2.38 (s, 3H), 3.20-3.30 (br s, 1H), 7.88-8.15 (m, 3H), 8.32-8.33 (br m, 1H)

Example 72 (Compound 75)

15 [0133]

Step 1: In a manner similar to that in Step 1 of Example 1, 2',6'-dimethoxyacetophenone=thiosemicarbazone (747 mg, 83%) was obtained from 2',6'-dimethoxyacetophenone (606 mg, 3.98 mmol) and thiosemicarbazide (374 mg, 4.09 mmol).

20 ¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.09 (s, 3H), 3.77 (s, 6H), 6.80 (d, J = 8.2 Hz, 2H), 7.44 (t, J = 8.2 Hz, 1H), 7.83 (br s, 1H), 8.04 (br s, 1H), 8.31 (br s, 1H)

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 75 (441 mg, 89%) was obtained from 2',6'-dimethoxyacetophenone=thiosemicarbazone (363 mg, 1.61 mmol) prepared above.

25 ¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.02 (s, 3H), 2.21 (s, 3H), 2.51 (s, 3H), 3.78 (s, 6H), 6.53 (d, J = 8.5 Hz, 2H), 7.15 (t, J = 8.5 Hz, 1H), 8.70 (br s, 1H)

Example 73 (Compound 76)

30 [0134]

Step 1: In a manner similar to that in Step 1 of Example 1, 3',5'-dihydroxyacetophenone=thiosemicarbazone (707 mg, 78%) was obtained from 3',5'-dihydroxyacetophenone (613 mg, 4.03 mmol) and thiosemicarbazide (376 mg, 4.11 mmol).

35 ¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.20 (s, 3H), 6.25 (br s, 1H), 6.69 (br s, 2H), 7.64 (br s, 1H), 8.26 (br s, 1H), 9.29 (br s, 2H), 10.19 (br s, 1H)

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 76 (591 mg, 69%) was obtained from 3',5'-dihydroxyacetophenone=thiosemicarbazone (622 mg, 2.76 mmol) prepared above.

40 ¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.01 (s, 3H), 2.17 (s, 3H), 2.18 (s, 3H), 6.10 (br s, 1H), 6.16 (br s, 2H), 9.27 (br s, 2H), 11.59 (br s, 1H)

Example 74 (Compound 77)

45 [0135]

Step 1: In a manner similar to that in Step 1 of Example 1, 3',4'-dihydroxyacetophenone=thiosemicarbazone (747 mg, 83%) was obtained from 3',4'-dihydroxyacetophenone (606 mg, 3.98 mmol) and thiosemicarbazide (374 mg, 4.09 mmol).

50 ¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.20 (s, 3H), 6.72 (br d, J = 8.3 Hz, 1H), 7.18 (br d, J = 8.3 Hz, 1H), 7.29 (br s, 1H), 7.65 (br s, 1H), 8.18 (br s, 2H), 9.09 (br s, 2H), 10.09 (br s, 1H)

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 77 (441 mg, 89%) was obtained from 3',4'-dihydroxyacetophenone=thiosemicarbazone (363 mg, 1.61 mmol) prepared above.

55 ¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.01 (s, 3H), 2.06 (s, 3H), 2.20 (s, 3H), 6.62 (br t, J = 7.6 Hz, 1H), 6.66 (br d, J = 8.2 Hz, 1H), 6.71 (br s, 1H), 8.93 (s, 1H), 8.97 (s, 1H), 11.58 (br s, 1H)

Example 75 (Compound 78)

[0136]

5 Step 1: In a manner similar to that in Step 1 of Example 1, 2',4'-dimethylacetophenone=thiosemicarbazone (110 mg, 12%) was obtained from 2',4'-dimethylacetophenone (598 mg, 4.04 mmol) and thiosemicarbazide (366 mg, 4.00 mmol).

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 78 (107 mg, 77%) was obtained from 2',4'-dimethylacetophenone=thiosemicarbazone (100 mg, 0.452 mmol) prepared above.

10 ¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.16 (s, 3H), 2.21 (s, 3H), 2.35 (s, 3H), 6.92 (d, J = 7.9 Hz, 1H), 7.07 (d, J = 7.9 Hz, 1H), 8.22 (br s, 1H)

Example 76 (Compound 79)

15 [0137]

Step 1: To a solution of hydrazine monohydrate (1.00 mL, 20.6 mmol) in acetonitrile (5.00 mL) was added allyl isothiocyanate (2.00 mL, 20.4 mmol), and the mixture was stirred at 60°C for 30 minutes. To the reaction mixture was added diethyl ether (50 mL), and the deposited solid was collected by filtration. The collected solid was dried to obtain 4-allylthiosemicarbazide (1.22 g, 46%).

20 ¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 4.11 (t, J = 5.3 Hz, 2H), 4.47 (br s, 2H), 5.03 (d, J = 12.3 Hz, 1H), 5.08 (d, J = 19.1 Hz, 1H), 5.86 (m, 1H), 7.88 (br s, 1H), 8.70 (br s, 1H)

Step 2: In a manner similar to that in Step 1 of Example 1, acetophenone=4-allylthiosemicarbazone (1.74 g, 80%) was obtained from acetophenone (1.09 mL, 9.34 mmol) and 4-allylthiosemicarbazide (1.22 g, 9.31 mmol) prepared above.

25 ¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.31 (s, 3H), 4.25 (t, J = 5.8 Hz, 2H), 5.10 (d, J = 10.5 Hz, 1H), 5.18 (d, J = 17.5 Hz, 1H), 5.91 (m, 1H), 7.37-7.42 (m, 3H), 7.91-7.94 (m, 2H), 8.81 (t, J = 6.0 Hz, 1H), 10.3 (br s, 1H)

Step 3: Acetophenone=4-allylthiosemicarbazone (30 mg, 0.11 mmol) prepared above was dissolved in chloroform (0.5 mL), and to the solution was added acetyl chloride (0.17 mL, 2.32 mmol) and pyridine (0.190 mL, 2.31 mmol), and the solution was stirred at room temperature for 5 hours. To the reaction mixture was added 2 mol/L aqueous sodium hydroxide, then the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous ammonium chloride and saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/2) to obtain Compound 79 (25 mg, 89%).

30 ¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.26 (s, 3H), 2.27 (s, 3H), 2.36 (s, 3H), 4.47-4.53 (m, 2H), 5.24 (d, J = 17.3 Hz, 1H), 5.29 (d, J = 10.5 Hz, 1H), 5.91 (m, 1H), 7.20-7.45 (m, 5H)

FAB-MS (m/z): 318 (M⁺+1)

Example 77 (Compounds 80 and 81)

40

[0138]

Step 1: In a manner similar to that in Step 3 of Example 76, Compound 80 (42 mg, 5%) was obtained from acetophenone=4-allylthiosemicarbazone (694 mg, 2.97 mmol) prepared in Step 2 of Example 76, isobutyryl chloride (0.83 mL, 5.97 mmol) and pyridine (0.43 mL, 5.28 mmol).

45 ¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.10 (d, J = 6.8 Hz, 3H), 1.13 (d, J = 6.9 Hz, 3H), 2.39 (s, 3H), 3.25 (quin., J = 7.0 Hz, 1H), 3.84-4.00 (m, 3H), 5.19 (d, J = 10.2 Hz, 1H), 5.26 (d, J = 17.2 Hz, 1H), 5.93 (m, 1H), 7.20-7.49 (m, 5H)

Step 2: In a manner similar to that in Example 15, Compound 81 (527 mg, 74%) was obtained from Compound 80 (623 mg, 2.05 mmol) prepared above, acetyl chloride (0.59 mL, 8.30 mmol) and pyridine (0.77 mL, 8.28 mmol).

50 ¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.10 (d, J = 6.9 Hz, 3H), 1.12 (d, J = 6.9 Hz, 3H), 2.27 (s, 3H), 2.34 (s, 3H), 3.21 (quin., J = 6.9 Hz, 1H), 4.51 (br s, 2H), 5.25 (d, J = 17.2 Hz, 1H), 5.30 (d, J = 10.7 Hz, 1H), 5.93 (m, 1H), 7.20-7.42 (m, 5H)

AP-MS (m/z): 346 (M⁺+1)

55 Example 78 (Compound 82)

[0139] In a manner similar to that in Step 3 of Example 76, Compound 82 (269 mg, 47%) was obtained from acetophenone=thiosemicarbazone (306 mg, 1.59 mmol) prepared in Step 1 of Example 1, pivaloyl chloride (0.40 mL, 3.21

mmol) and pyridine (0.26 mL, 3.22 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.29 (s, 9H), 1.30 (s, 9H), 2.35 (s, 3H), 7.20-7.46 (m, 5H), 7.90 (m, 1H)

AP-MS (m/z): 360 (M⁺-1)

5 Example 79 (Compounds 83 and 84)

[0140]

10 Step 1: In a manner similar to that in Example 12, Compound 83 (537 mg, 67%) was obtained from Compound 21 (1.00 g, 2.88 mmol) prepared in Example 18.

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.12 (d, J = 6.9 Hz, 3H), 1.14 (d, J = 6.9 Hz, 3H), 2.39 (s, 3H), 2.91 (d, J = 4.9 Hz, 3H), 3.30 (m, 1H), 3.90 (br, 1H), 7.20-7.43 (m, 5H)

Step 2: In a manner similar to that in Example 15, Compound 84 (233 mg, 38%) was obtained from Compound 83 (536 mg, 1.93 mmol) prepared above, acetyl chloride (0.28 mL, 3.87 mmol) and pyridine (0.32 mL, 3.90 mmol).

15 ¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.12 (d, J = 6.9 Hz, 3H), 1.14 (d, J = 6.9 Hz, 3H), 2.28 (s, 3H), 2.34 (s, 3H), 3.28 (quin., J = 6.9 Hz, 1H), 3.46 (br s, 3H), 7.20-7.43 (m, 5H) FAB-MS (m/z): 320 (M⁺+1)

Elemental analysis (C₁₈H₂₁N₃O₂S): Found (%) C; 60.16, H; 6.63, N; 13.15, Calcd. (%) C; 60.27, H; 6.73, N; 13.20

20 Example 80 (Compound 85)

[0141] In a manner similar to that in Step 2 of Example 1, Compound 85 (176 mg, 20%) was obtained from acetophenone=thiosemicarbazone (517 mg, 2.68 mmol) prepared in Step 1 of Example 1 and isobutyric anhydride (2.22 mL, 13.4 mmol).

25 ¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.09 (d, J = 2.6 Hz, 3H), 1.12 (d, J = 2.6 Hz, 3H), 1.21 (d, J = 2.6 Hz, 3H), 1.23 (d, J = 2.6 Hz, 3H), 2.37 (s, 3H), 2.50 (quin., J = 6.9 Hz, 1H), 3.20 (quin., J = 6.9 Hz, 1H), 7.20-7.48 (m, 5H), 7.98 (br s, 1H) AP-MS (m/z): 334 (M⁺+1)

Elemental analysis (C₁₇H₂₃N₃O₂S): Found (%) C; 61.23, H; 6.95, N; 12.60, Calcd. (%) C; 61.22, H; 6.93, N; 12.63

30 Example 81 (Compounds 86 and 87)

[0142]

35 Step 1: In a manner similar to that in Example 11, Compound 86 (588 mg, 43%) was obtained from acetophenone=thiosemicarbazone (1.01 g, 5.22 mmol) prepared in Step 1 of Example 1, isobutyric anhydride (1.73 mL, 10.4 mmol) and pyridine (0.84 mL, 10.4 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.09 (d, J = 6.9 Hz, 3H), 1.11 (d, J = 6.9 Hz, 3H), 2.40 (s, 3H), 3.21 (quin., J = 6.9 Hz, 1H), 4.12 (br s, 2H), 7.20-7.40 (m, 5H)

Step 2: In a manner similar to that in Example 15, Compound 87 (47 mg, 16%) was obtained from Compound 86 (256 mg, 0.97 mmol) prepared above and acetic anhydride (0.46 mL, 4.88 mmol).

40 ¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.19 (d, J = 6.9 Hz, 3H), 1.20 (d, J = 6.9 Hz, 3H), 2.25 (s, 3H), 2.38 (s, 3H), 2.47 (quin., J = 6.9 Hz, 1H), 7.20-7.50 (m, 5H)

Example 82 (Compound 88)

45 [0143] In a manner similar to that in Example 15, Compound 88 (53 mg, 8%) was obtained from Compound 14 (502 mg, 2.14 mmol) prepared in Example 11 and isobutyric anhydride (1.77 mL, 10.7 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.20 (d, J = 6.9 Hz, 3H), 1.22 (d, J = 6.9 Hz, 3H), 2.24 (s, 3H), 2.38 (s, 3H), 2.48 (quin., J = 6.9 Hz, 1H), 7.20-7.46 (m, 5H), 8.08 (br s, 1H) AP-MS (m/z): 306 (M⁺+1)

50 Example 83 (Compound 89)

[0144] In a manner similar to that in Example 15, Compound 89 (274 mg, 64%) was obtained from Compound 14 (303 mg, 1.29 mmol) prepared in Example 11, cyclopentanecarbonyl chloride (0.32 mL, 2.59 mmol) and pyridine (0.21 mL, 2.60 mmol).

55 ¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.50-1.95 (m, 8H), 2.24 (s, 3H), 2.38 (s, 3H), 2.65 (quin., J = 7.9 Hz, 1H), 7.20-7.45 (m, 5H), 8.04 (br s, 1H)

AP-MS (m/z): 330 (M⁺-1)

Elemental analysis (C₁₇H₂₁N₃O₂S-0.4H₂O): Found (%) C; 60.30, H; 6.49, N; 12.41, Calcd. (%) C; 60.45, H; 6.49, N;

12.05

Example 84 (Compounds 90 and 91)

5 [0145]

Step 1: In a manner similar to that in Example 11, Compound 90 (123 mg, 13%) was obtained from acetophenone=thiosemicarbazone (507 mg, 2.63 mmol) prepared in Step 1 of Example 1, isovaleric anhydride (1.05 mL, 5.30 mmol) and pyridine (0.43 mL, 5.26 mmol).

10 ^1H NMR (270 MHz, CDCl_3) δ (ppm): 0.82-1.00 (m, 6H), 2.12 (quin., $J = 6.6$ Hz, 1H), 2.38 (s, 3H), 2.45 (d, $J = 7.7$ Hz, 2H), 4.34 (br, 2H), 7.20-7.48 (m, 5H)

Step 2: In a manner similar to that in Example 15, Compound 91 (128 mg, 98%) was obtained from Compound 91 (105 mg, 0.38 mmol) prepared above, isobutyryl chloride (0.08 mL, 0.76 mmol) and pyridine (0.08 mL, 0.80 mmol).

15 ^1H NMR (270 MHz, CDCl_3) δ (ppm): 0.92 (d, $J = 6.6$ Hz, 1H), 0.93 (d, $J = 6.6$ Hz, 1H), 1.18 (d, $J = 3.3$ Hz, 1H), 1.21 (d, $J = 3.3$ Hz, 1H), 2.13 (quin., $J = 6.6$ Hz, 1H), 2.38 (s, 3H), 2.39-2.56 (m, 4H), 7.20-7.48 (m, 5H), 8.15 (br s, 1H)

Example 85 (Compound 92)

20

[0146]

Step 1: To a solution of acetophenone (4.00 mL, 34.3 mmol) in ethanol (15 mL) was added hydrazine monohydrate (6.67 mL, 138 mmol), and the mixture was heated under reflux for 4 hours. After cooling, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/2) to obtain acetophenone=hydrazone (5.39 g, ~100%).

25 ^1H NMR (300 MHz, CDCl_3) δ (ppm): 2.00 (s, 3H), 5.34 (br s, 2H), 7.22-7.60 (m, 5H) ^{13}C NMR (300 MHz, CDCl_3) δ (ppm): 11.3, 125.1, 127.7, 127.9, 139.1, 146.7

Step 2: To a solution of ammonium thiocyanate (3.40 g, 44.6 mmol) in acetone (20 mL) was added acetyl chloride (2.80 mL, 37.1 mmol), and the mixture was stirred at 70°C for 10 minutes. To the reaction mixture was added acetophenone=hydrazone (5.36 g, 40.0 mmol) prepared above, and the mixture was heated under reflux for 20 minutes. After the reaction mixture was cooled, saturated aqueous ammonium chloride was added to the mixture, and the mixture was extracted with chloroform. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/2) to obtain acetophenone=4-acetylthiosemicarbazone (148mg, 2%).

30 ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ (ppm): 2.15 (s, 3H), 2.28 (s, 3H), 7.47-7.51 (m, 3H), 7.56-7.59 (m, 2H), 11.6 (br s, 1H), 13.6 (br s, 1H)

Step 3: In a manner similar to that in Step 3 of Example 76, Compound 92 (36 mg, 88%) was obtained from acetophenone=4-acetylthiosemicarbazone (30 mg, 0.13 mmol) prepared above, pivaloyl chloride (32 μL , 0.26 mmol) and pyridine (20 μL , 0.26 mmol).

35 ^1H NMR (300 MHz, CDCl_3) δ (ppm): 1.27 (s, 9H), 2.25 (s, 3H), 2.38 (s, 3H), 7.23-7.46 (m, 5H), 8.13 (br s, 1H)
 40 ^{13}C NMR (300 MHz, CDCl_3) δ (ppm): 24.0, 27.2, 39.4, 80.5, 125.1, 128.0, 128.6, 143.0, 143.1, 169.0, 178.7
 AP-MS (m/z): 318 ($M^+ + 1$)

Example 86 (Compound 93)

50 [0147] In a manner similar to that in Step 2 of Example 1, Compound 93 (123 mg, 45%) was obtained from Compound 14 (201 mg, 0.853 mmol) prepared in Example 11 and pivaloyl chloride (0.21 mL, 1.71 mmol).

^1H NMR (270 MHz, CDCl_3) δ (ppm): 1.26 (s, 9H), 2.24 (s, 3H), 2.38 (s, 3H), 7.20-7.51 (m, 5H), 8.10 (br s, 1H)

AP-MS (m/z): 319 ($M^+ + 1$)

55

Example 87 (Compound 94)

[0148]

- 5 Step 1: In a manner similar to that in Step 1 of Example 1, propiophenone=thiosemicarbazone (759 mg, 88%) was obtained from propiophenone (382 mg, 4.18 mmol) and thiosemicarbazide (541 mg, 3.92 mmol).
 Step 2: In a manner similar to that in Step 3 of Example 76, Compound 94 (270 mg, 58%) was obtained from propiophenone=thiosemicarbazone (256 mg, 1.24 mmol) prepared above, pivaloyl chloride (597 μ L, 4.84 mmol) and pyridine (391 μ L, 4.84 mmol).
 10 ^1H NMR (270 MHz, CDCl_3) δ (ppm): 1.15 (dd, J = 7.1, 7.3 Hz, 3H), 1.29 (s, 9H), 1.34 (s, 9H), 2.29 (qd, J = 7.3, 14.6 Hz, 1H), 3.10 (qd, J = 7.1, 14.6 Hz, 1H), 7.21-7.40 (m, 5H), 8.31 (br s, 1H)
 AP-MS (m/z): 377 ($\text{M}^+ + 1$)

Example 88 (Compound 95)

15

[0149]

- 20 Step 1: 2-Aminoacetophenone hydrochloride (6.10 g, 35.5 mmol) was dissolved in dichloromethane (60 mL), and to the solution was added triethylamine (7.56 g, 74.9 mmol). The solution was cooled to 0°C, and to the solution was added methanesulfonyl chloride (2.84 mL, 36.5 mmol). The solution was stirred at the same temperature for 5 minutes, and then at room temperature for 2 hours. To the reaction mixture was added water and 1 mol/L hydrochloric acid, and the mixture was extracted with chloroform. After the organic layer was dried over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure. The residue was suspended in chloroform (5 mL) and the suspension was stirred, and then, the resulted crystals were collected by filtration to obtain 2-(methylsulfonylamino)acetophenone (4.58 g, 57%).
 25 Step 2: In a manner similar to that in Step 1 of Example 1, 2-(methylsulfonylamino)acetophenone=thiosemicarbazone (3.08 g, 51%) was obtained from 2-(methylsulfonylamino)acetophenone (4.58 g, 20.2 mmol) prepared above and thiosemicarbazide (1.84 g, 20.2 mmol).
 Step 3: In a manner similar to that in Step 3 of Example 76, Compound 95 (1.81 g, 91%) was obtained from 2-(methylsulfonylamino)acetophenone=thiosemicarbazone (1.31 g, 4.36 mmol) prepared above, pivaloyl chloride (2.10 g, 17.4 mmol) and pyridine (1.38 g, 17.4 mmol).
 30 ^1H NMR (270 MHz, CDCl_3) δ (ppm): 1.30 (s, 9H), 1.36 (s, 9H), 2.97 (s, 3H), 3.98 (dd, J = 5.3, 13.8 Hz, 1H), 4.64 (dd, J = 8.5, 13.8 Hz, 1H), 5.10 (br dd, J = 5.3, 8.5 Hz, 1H), 7.25-7.39 (m, 5H), 7.93 (br s, 1H)
 AP-MS (m/z): 453 ($\text{M}^+ - 1$)

35

Example 89 (Compound 96)

[0150]

- 40 Step 1: In a manner similar to that in Step 1 of Example 1, 2-(methylsulfonylamino)acetophenone=4-methylthiosemicarbazone (122 mg) was obtained from 2-(methylsulfonylamino)acetophenone (209 mg, 0.98 mmol) prepared in Step 1 of Example 88 and 4-methylthiosemicarbazide (106 mg, 1.00 mmol).
 Step 2: In a manner similar to that in Step 3 of Example 76, Compound 96 (68 mg, 15%) was obtained from 2-(methylsulfonylamino)acetophenone=4-methylthiosemicarbazone (122 mg, 0.41 mmol) obtained above, pivaloyl chloride (128 μ L, 1.04 mmol) and pyridine (80 μ L, 1.04 mmol).
 45 ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ (ppm): 1.27 (s, 3H), 1.28 (s, 3H), 2.95 (s, 3H), 3.53 (s, 3H), 3.94 (dd, J = 13.9, 6.4 Hz, 1H), 4.27 (dd, J = 13.9, 7.9 Hz, 1H), 7.11 (t, J = 7.2 Hz, 1H), 7.21-7.38 (m, 5H)
 AP-MS (m/z): 467 ($\text{M}^+ - 1$)

50 Example 90 (Compound 97)

[0151]

- 55 Step 1: In a manner similar to that in Step 1 of Example 88, 2-(ethylsulfonylamino)acetophenone (367 mg, 39%) was obtained from 2-aminoacetophenone hydrochloride (714 mg, 4.16 mmol), triethylamine (1.45 mL, 10.4 mmol) and ethanesulfonyl chloride (0.434 mL, 4.58 mmol).
 Step 2: In a manner similar to that in Step 1 of Example 1, 2-(ethylsulfonylamino)acetophenone=thiosemicarbazone (327 mg, 43%) was obtained from 2-(ethylsulfonylamino)acetophenone (367 mg, 1.61 mmol) prepared above and

thiosemicarbazide (147 mg, 1.61 mmol).

Step 3: In a manner similar to that in Step 2 of Example 1, Compound 97 (39 mg, 25%) was obtained from 2-(ethylsulfonylamino)acetophenone=thiosemicarbazone (99 mg, 0.330 mmol), pivaloyl chloride (162 μ L, 1.32 mmol) and pyridine (130 μ L, 1.58 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.26 (s, 9H), 1.28 (t, J = 7.8 Hz, 3H), 1.29 (s, 9H), 3.09 (m, 2H), 3.97 (dd, J = 5.1, 13.5 Hz, 1H), 4.60 (dd, J = 8.1, 13.5 Hz, 1H), 4.99 (br dd, J = 5.1, 8.1 Hz, 1H), 7.25-7.38 (br s, 5H), 7.93 (br s, 1H)

Example 91 (Compound 98)

[0152]

Step 1: In a manner similar to that in Step 1 of Example 1, 2-methoxyacetophenone=thiosemicarbazone (367 mg, 62%) was obtained from 2-methoxyacetophenone (288 mg, 1.92 mmol) and thiosemicarbazide (179 mg, 1.96 mmol).

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 98 (132 mg, 59%) was obtained from 2-methoxyacetophenone=thiosemicarbazone (128 mg, 0.573 mmol) prepared above, pivaloyl chloride (211 μ L, 1.72 mmol) and pyridine (152 μ L, 1.88 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.28 (s, 9H), 1.32 (s, 9H), 3.51 (s, 3H), 4.36 (d, J = 9.6 Hz, 1H), 4.48 (d, J = 9.6 Hz, 1H), 7.24-7.38 (m, 5H), 7.88 (s, 1H)

AP-MS (m/z): 392 (M⁺+1)

Example 92 (Compound 99)

[0153]

Step 1: Methane sulfonamide (0.476 g, 5.00 mmol) was dissolved in N,N-dimethylformamide (10 mL), and to the solution was added 60% sodium hydride (0.275 g, 5.00 mmol) and the mixture was stirred in a water bath for 20 minutes. To the reaction mixture was added 3-chloropropiophenone (843 mg, 5.00 mol). The mixture was stirred in a water bath for one hour, and further stirred at room temperature for 15 hours. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride and dried over anhydrous sodium sulfate, and then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol = 20/1) to obtain 3-(methylsulfonylamino)propiophenone (240 mg, 21%).

Step 2: In a manner similar to that in Step 1 of Example 1, 3-(methylsulfonylamino)propiophenone=thiosemicarbazone (219 mg, 45%) was obtained from 3-(methylsulfonylamino)propiophenone (388 mg, 1.71 mmol) prepared above and thiosemicarbazide (156 mg, 1.71 mmol).

Step 3: In a manner similar to that in Step 2 of Example 1, Compound 99 (218 mg, 86%) was obtained from 3-(methylsulfonylamino)propiophenone=thiosemicarbazone (200 mg, 0.696 mmol) obtained above, pivaloyl chloride (342 μ L, 2.78 mmol) and pyridine (219 μ L, 2.78 mmol).

¹H NMR (300 MHz, CDCl₃) δ (ppm): 1.30 (s, 9H), 1.34 (s, 9H), 2.56-2.65 (m, 1H), 2.94 (s, 3H), 3.21-3.44 (m, 2H), 3.58-3.70 (m, 1H), 4.45 (br s, 1H), 7.28-7.37 (m, 5H), 7.97 (br s, 1H)

AP-MS (m/z): 467 (M⁻-1)

Example 93 (Compound 100)

[0154] In a manner similar to that in Step 3 of Example 76, an oily compound was obtained from 3-(methylsulfonylamino)propiophenone=thiosemicarbazone (173 mg, 0.604 mmol) prepared in Step 2 of Example 92, isobutyryl chloride (316 μ L, 3.02 mmol) and pyridine (292 μ L, 3.62 mmol). The oily compound was dissolved in methanol (10 mL). To the solution was added potassium carbonate (1.00 g, 7.24 mmol), and the mixture was vigorously stirred for 1 hour. The reaction mixture was filtered, and the filtrate was concentrated. And then, to the concentrate was added chloroform, water and 1.0 mol/L hydrochloric acid, and the solution was extracted with chloroform. The organic layer was washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by preparative thin layer chromatography (chloroform/methanol = 20/1) to obtain Compound 100 (111 mg, 41%).

¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 0.99-1.07 (m, 12H), 2.55-2.66 (m, 2H), 2.80-3.00 (m, 1H), 2.89 (s, 3H), 3.05-3.17 (m, 1H), 3.24-3.38 (m, 2H), 7.15 (br t, J = 5.9 Hz, 1H), 7.24-7.39 (m, 5H), 11.6 (br s, 1H)

Example 94 (Compound 101)

[0155]

- 5 Step 1: In a manner similar to that in Step 1 of Example 88, 2-(trifluoroacetyl-amino)acetophenone (4.38 g, 59%) was obtained from 2-aminoacetophenone hydrochloride (5.47 g, 31.9 mmol), triethylamine (11.1 mL, 80.0 mmol) and trifluoroacetic anhydride (4.96 mL, 35.1 mmol).
- Step 2: In a manner similar to that in Step 1 of Example 1, 2-(trifluoroacetyl-amino)acetophenone=thiosemicarbazone was obtained from 2-(trifluoroacetyl-amino)acetophenone (3.00 g, 13.0 mmol) prepared above and thiosemicarbazide (1.18 g, 13.0 mmol).
- 10 Step 3: In a manner similar to that in Step 3 of Example 76, Compound 101 (1.72 g, 28%) was obtained from 2-(trifluoroacetyl-amino)acetophenone=thiosemicarbazone prepared above, pivaloyl chloride (50 mmol, 6.16 mL) and pyridine (60.0 mmol, 4.85 mL).
- ¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.27 (s, 9H), 1.38 (s, 9H), 3.95 (dd, J = 3.0, 13.5 Hz, 1H), 4.89 (dd, J = 3.7, 13.5 Hz, 1H), 7.15 (br d, J = 7.3 Hz, 2H), 7.30-7.40 (m, 3H), 7.92 (br s, 1H), 8.27 (br s, 1H)
- 15 AP-MS (m/z): 471 (M⁺-1)

Example 95 (Compound 102)

- 20 [0156] In a manner similar to that in Step 3 of Example 76, Compound 102 (64.6 mg, 39%) was obtained from 2-(methylsulfonyl-amino)acetophenone=thiosemicarbazone (100 mg, 0.333 mmol) prepared in Step 2 of Example 88, isobutyl chloride (140 μL, 1.33 mmol) and pyridine (108 μL, 1.33 mmol).
- ¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.17 (d, J = 6.9 Hz, 3H), 1.19 (d, J = 6.9 Hz, 3H), 1.25 (d, J = 6.9 Hz, 6H), 1.29 (d, J = 6.9 Hz, 6H), 3.05 (s, 3H), 3.10-3.30 (m, 3H), 4.01 (dd, J = 4.8, 14.2 Hz, 1H), 4.74 (dd, J = 7.8, 14.2 Hz, 1H), 5.37 (br s, 1H), 7.26-7.40 (m, 5H)
- 25

Example 96 (Compound 103)

- [0157] Compound 102 (40.0 mg, 0.0805 mmol) prepared in Example 95 was dissolved in methanol (10 mL). To the solution was added potassium carbonate (1.00 g, 7.24 mmol), and the mixture was vigorously stirred for 1 hour. The reaction mixture was filtered, and the filtrate was concentrated. Then, to the residue was added chloroform, 1 mol/L hydrochloric acid and water, and the mixture was extracted with chloroform. The organic layer was washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by preparative thin layer chromatography (chloroform/methanol = 20/1) to obtain
- 35 Compound 103 (24.2 mg, 84%).
- ¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.13 (d, J = 6.9 Hz, 3H), 1.18 (d, J = 6.9 Hz, 3H), 1.21 (d, J = 6.9 Hz, 3H), 1.23 (d, J = 6.9 Hz, 3H), 2.50 (m, 1H), 2.90 (s, 3H), 3.27 (m, 1H), 3.98 (dd, J = 5.0, 13.9 Hz, 1H), 4.60 (dd, J = 8.2, 13.9 Hz, 1H), 5.35 (br dd, J = 5.0, 8.2 Hz, 1H), 7.26-7.40 (m, 5H), 8.02 (br s, 1H)

Example 97 (Compound 104)

[0158]

- 45 Step 1: In a manner similar to that in Step 1 of Example 1, 3-(dimethyl-amino)propiophenone=thiosemicarbazone (491 mg, 46%) was obtained from 3-(dimethyl-amino)propiophenone (910 mg, 4.28 mmol) and thiosemicarbazide (387 mg, 4.25 mmol).
- Step 2: In a manner similar to that in Step 3 of Example 76, Compound 104 (116 mg, 33%) was obtained from 3-(dimethyl-amino)propiophenone=thiosemicarbazone (210 mg, 0.839 mmol) prepared above, pivaloyl chloride (496 μL, 3.78 mmol) and pyridine (326 μL, 3.78 mmol).
- 50 ¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.29 (s, 9H), 1.31 (s, 9H), 2.23-2.29 (m, 1H), 2.26 (br s, 3H), 2.27 (br s, 3H), 2.46 (ddd, J = 8.8, 4.3, 11.3 Hz, 1H), 2.87 (m, 1H), 3.31 (m, 1H), 7.20-7.36 (m, 5H), 7.90 (br s, 1H)

Example 98 (Compound 105)

[0159]

- 55 Step 1: In a manner similar to that in Step 2 of Example 1, 3-carbomethoxypropiophenone=thiosemicarbazone (10.6 g, 94%) was obtained from 3-carbomethoxypropiophenone (8.13 g, 42.3 mmol) and thiosemicarbazide (3.88

g, 42.3 mmol).

Step 2: In a manner similar to that in Step 3 of Example 76, Compound 105 (9.70 g, 77%) was obtained from 3-carbomethoxypropiofenone=thiosemicarbazone (7.76 g, 29.2 mmol) prepared above, pivaloyl chloride (14.4 mL, 117 mmol) and pyridine (11.3 mL, 140 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.29 (s, 9H), 1.32 (s, 9H), 2.37 (m, 1H), 2.67 (m, 1H), 2.79 (m, 1H), 3.42 (m, 1H), 3.70 (s, 3H), 7.22-7.40 (m, 5H), 7.89 (br s, 1H)

Example 99 (Compound 106)

[0160] Sodium hydroxide (2.7g, 67 mmol) was dissolved in water (23 mL). Subsequently, to the solution was added methanol (30 mL) and the solution was stirred. To the solution was added Compound 105 (9.65 g, 22.3 mmol) prepared in Example 98, and the mixture was stirred at room temperature for 5 hours. To the reaction mixture was added 1 mol/L hydrochloric acid (20 mL) and water (30 mL), and the deposited white crystals were collected by filtration. The resulting crystals were washed with water and diisopropyl ether, and then, dried under reduced pressure to obtain Compound 106 (8.92 g, 96%).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.30 (s, 9H), 1.33 (s, 9H), 2.00-2.51 (br s, 1H), 2.44 (m, 1H), 2.66 (m, 1H), 2.88 (m, 1H), 3.44 (m, 1H), 7.23-7.40 (m, 5H), 7.92 (br s, 1H)

Example 100 (Compound 107)

[0161] Compound 106 (1.21 g, 2.88 mmol) prepared in Example 99 was cooled to 0°C. Oxalyl chloride (5 mL) was added to the compound, and the solution was allowed to react at 0°C for 1 hour. The solvent was evaporated under reduced pressure, and the residue was dried in vacuo. To the residue was added tetrahydrofuran, and the mixture was stirred at 0°C. Then, to the reaction mixture was added 4 mol/L ammonia-methanol solution (5 mL, 20 mmol), and the mixture was stirred at room temperature for 3 hours. To the reaction mixture was added 1 mol/L hydrochloric acid (20 mL) and water (30 mL), and extracted with chloroform. The organic layer was washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. After the solvent was evaporated under reduced pressure, to the resulting residue was added diisopropyl ether, and then the deposited white crystals were collected by filtration. The resulting crystals were washed with water and diisopropyl ether, and then dried under reduced pressure to obtain Compound 107 (8.92 g, 96%).

¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 1.17 (s, 9H), 1.28 (s, 9H), 1.81-2.03 (m, 1H), 2.15-2.30 (m, 1H), 2.49-2.75 (m, 1H), 2.95-3.20 (m, 1H), 6.80 (br s, 1H), 7.20-7.41 (m, 5H), 10.93 (br s, 2H)

Example 101 (Compound 108)

[0162] In a manner similar to that in Example 100, Compound 108 (65 mg, 60%) was obtained from Compound 106 (0.104 g, 0.248 mmol) prepared in Example 99, oxalyl chloride (5 mL), hydroxylamine hydrochloride (0.017 g, 0.245 mmol) and triethylamine (0.062 g, 0.614 mmol).

APCI-MS (m/z): 433 (M⁺-1)

Example 102 (Compound 109)

[0163] In a manner similar to that in Example 100, Compound 109 (1.08 g, 87%) was obtained from Compound 106 (1.20 g, 2.86 mmol) prepared in Example 99, oxalyl chloride (5 mL) and 4 mol/L methylamine-methanol solution (10 mL, 40 mmol).

AP-MS (m/z): 431 (M⁺-1)

Example 103 (Compound 110)

[0164]

Step 1: In a manner similar to that in Step 1 of Example 1, 3-(dimethylaminocarbonyl)propiofenone=thiosemicarbazone (3.67 g, 79%) was obtained from 3-(dimethylaminocarbonyl)propiofenone (4.00 g, 18.7 mmol) and thiosemicarbazide (1.70 g, 18.7 mmol).

Step 2: In a manner similar to that in Step 3 of Example 76, Compound 110 (1.64 g, 49%) was obtained from 3-(dimethylaminocarbonyl)propiofenone=thiosemicarbazone (2.00 g, 7.99 mmol) prepared above, pivaloyl chloride (3.94 mL, 32.0 mmol) and pyridine (3.11 mL, 38.4 mmol).

AP-MS (m/z): 447 (M⁺+1)

Example 104 (Compound 111)

[0165] In a manner similar to that in Example 100, Compound 111 (480 mg, 84%) was obtained from Compound 106 (51.8 mg, 0.124 mmol) prepared in Example 99, oxalyl chloride (0.5 mL), ethanolamine (7.58 mg, 0.248 mmol) and triethylamine (18.8 mg, 0.186 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.29 (s, 9H), 1.33 (s, 9H), 2.16-2.25 (m, 1H), 2.65-2.79 (m, 2H), 3.33-3.44 (m, 3H), 3.72 (m, 2H), 6.18 (br s, 1H), 7.22-7.35 (m, 6H), 8.01 (br s, 1H)

Example 105 (Compound 112)

[0166] In a manner similar to that in Example 100, Compound 112 (400 mg, 68%) was obtained from Compound 106 (51.8 mg, 0.124 mmol) prepared in Example 99, oxalyl chloride (0.5 mL), n-butylamine (18.14 mg, 0.248 mmol) and triethylamine (18.8 mg, 0.186 mmol).

¹H NMR (300 MHz, CDCl₃) δ (ppm): 0.92 (t, J = 7.1 Hz, 3H), 1.25-1.60 (m, 4H), 1.29 (s, 9H), 1.33 (s, 9H), 2.16 (m, 1H), 2.69 (m, 2H), 3.25 (m, 2H), 3.67 (m, 1H), 5.62 (br s, 1H), 7.23-7.34 (m, 5H), 7.94 (br s, 1H)

Example 106 (Compound 113)

[0167] In a manner similar to that in Example 100, Compound 113 (50 mg, 81%) was obtained from Compound 106 (51.8 mg, 0.124 mmol) prepared in Example 99, oxalyl chloride (0.5 mL), cyclohexylamine (24.6 mg, 0.248 mmol) and triethylamine (18.8 mg, 0.186 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.05-1.50 (m, 6H), 1.28 (s, 9H), 1.33 (s, 9H), 1.65-1.80 (m, 2H), 1.85-1.95 (m, 2H), 2.14 (m, 1H), 2.65 (m, 2H), 3.37 (m, 1H), 3.38 (m, 1H), 5.50 (br s, 1H), 7.10-7.38 (m, 5H), 7.93 (br s, 1H)

Example 107 (Compound 114)

[0168]

Step 1: In a manner similar to that in Step 1 of Example 1, 4-carbomethoxybutyrophenone=thiosemicarbazone (0.700 g, 88%) was obtained from 4-carbomethoxybutyrophenone (0.588 g, 2.85 mmol) and thiosemicarbazide (0.260 g, 2.85 mmol).

Step 2: In a manner similar to that in Step 3 of Example 76, Compound 114 (318 mg, 64%) was obtained from 4-carbomethoxybutyrophenone=thiosemicarbazone prepared above, pivaloyl chloride (0.549 mL, 4.45 mmol) and pyridine (0.431 mL, 5.34 mmol).

¹H NMR (300 MHz, CDCl₃) δ (ppm): 1.29 (s, 9H), 1.32 (s, 9H), 1.51-1.60 (m, 1H), 2.10-2.30 (m, 2H), 2.44 (m, 2H), 3.03-3.17 (m, 1H), 3.68 (s, 3H), 7.20-7.36 (m, 5H), 7.95 (br s, 1H)

Example 108 (Compound 115)

[0169] In a manner similar to that in Example 99, Compound 115 (234 mg, 95%) was obtained from Compound 114 (254 mg, 0.567 mmol) prepared in Example 107, sodium hydroxide (70.0 mg, 1.75 mmol), water (2 mL) and ethanol (4 mL).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.29 (s, 9H), 1.32 (s, 9H), 1.65-1.75 (m, 1H), 2.10-2.35 (m, 2H), 2.50 (m, 2H), 3.10-3.20 (m, 1H), 7.23-7.35 (m, 6H), 7.92 (br s, 1H)

Example 109 (Compound 116)

[0170] In a manner similar to that in Example 100, Compound 116 (0.028 g, 55%) was obtained from Compound 115 (50.0 mg, 0.115 mmol) prepared in Example 108, oxalyl chloride (0.5 mL) and 40% methylamine-methanol solution (5 mL). ¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.29 (s, 9H), 1.32 (s, 9H), 1.50-1.65 (m, 1H), 2.21-2.35 (m, 4H), 2.80 (d, J = 4.8 Hz, 3H), 3.13 (m, 1H), 5.71 (br s, 1H), 7.20-7.35 (m, 5H), 7.97 (br s, 1H)

Example 110 (Compound 117)

[0171] In a manner similar to that in Example 100, Compound 117 (0.024 g, 47%) was obtained from Compound 115 (51.5 mg, 0.119 mmol) prepared in Example 108, oxalyl chloride (0.5 mL) and 4 mol/L ammonia-methanol solution (5 mL).

AP-MS (m/z): 431 (M-1)

Example 111 (Compound 118)

[0172] In a manner similar to that in Step 3 of Example 76, Compound 118 (302 mg, 26%) was obtained from 2-(methylsulfonylamino)acetophenone=thiosemicarbazone (1.00 g, 3.49 mmol) prepared in Step 2 of Example 88, acetic anhydride (659 μ L, 6.98 mmol) and pyridine (665 μ L, 6.98 mmol).

^1H NMR (270 MHz, CDCl_3) δ (ppm): 2.29 (s, 3H), 2.99 (s, 3H), 4.04 (d, J = 14.0 Hz, 1H), 4.55 (d, J = 14.0 Hz, 1H), 7.30-7.41 (m, 5H)

AP-MS (m/z): 329 ($\text{M}^+ + 1$)

Example 112 (Compound 119)

[0173] Compound 118 (10.6 mg, 0.0323 mmol) prepared in Example 111 was dissolved in tetrahydrofuran (80 mL). To the solution was added dimethylaminopyridine (7.9 mg, 0.0646 mmol) and pyridine (7.8 μ L, 0.0969 mmol), and the mixture was cooled to 0°C. To the solution was added pivaloyl chloride (20 μ L, 0.162 mmol), and the mixture was stirred at 0°C for 5 minutes, and further stirred at room temperature for 4 hours. To the reaction mixture was added water and 1 mol/L hydrochloric acid, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography (chloroform/methanol = 12/1) to obtain Compound 119 (5.3 mg, 40%).

^1H -NMR (270 MHz, CDCl_3) δ (ppm): 1.27 (s, 9H), 2.32 (s, 3H), 2.95 (s, 3H), 3.98 (dd, J = 5.2, 14.0 Hz, 1H), 4.60 (dd, J = 8.1, 13.9 Hz, 1H), 5.40 (m, 1H), 7.29-7.40 (m, 5H), 8.11 (br s, 1H)

Example 113 (Compound 120)

[0174] 2-(Methylsulfonylamino)acetophenone=thiosemicarbazone (300 mg, 1.05 mmol) prepared in Step 2 of Example 88 was dissolved in tetrahydrofuran (18 mL). To the solution was added 4-dimethylaminopyridine (641 mg, 5.25 mmol) and pivaloyl chloride (0.13 mL, 1.1 mmol), and the mixture was stirred at room temperature. To the mixture was further added, after 1 hour and after 2 hours each, pivaloyl chloride (0.065 mL, 0.53 mmol), and the mixture was stirred for 3.6 hours in total. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by preparative thin layer chromatography (chloroform/methanol = 20/1) to obtain Compound 120 (88 mg, yield 22%).

^1H NMR (270 MHz, CDCl_3) δ (ppm): 1.34 (s, 9H), 2.96 (s, 3H), 4.06 (dd, J = 6.2, 13.7 Hz, 1H), 4.19 (br s, 2H), 4.58 (dd, J = 7.0, 13.7 Hz, 1H), 5.20 (t, J = 6.4 Hz, 1H), 7.27-7.55 (m, 5H)

AP-MS (m/z): 371 ($\text{M}^+ + 1$)

Example 114 (Compound 121)

[0175] 6-Bromohexanoic acid (469 mg, 2.41 mmol) was dissolved in dichloromethane (15 mL). To the solution was added oxalyl chloride (0.28 mL, 3.2 mmol), and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated from the reaction mixture under reduced pressure, and the resulting residue was dissolved in dichloromethane (15 mL). To the solution was added Compound 120 (297 mg, 0.802 mmol) prepared in Example 113 and pyridine (0.20 mL, 2.4 mmol), and the mixture was stirred at room temperature for 1 hour. After the reaction mixture was concentrated under reduced pressure, water was added to the residue, and the solution was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by preparative thin layer chromatography (chloroform/methanol = 30/1) to obtain Compound 121 (315 mg, yield 72%).

^1H NMR (270 MHz, CDCl_3) δ (ppm): 1.32 (s, 9H), 1.50 (m, 2H), 1.67 (m, 2H), 1.86 (q, J = 6.7 Hz, 2H), 2.34 (t, J = 7.3 Hz, 2H), 2.98 (s, 3H), 3.40 (t, J = 6.6 Hz, 2H), 3.99 (dd, J = 5.2, 13.6 Hz, 1H), 4.63 (dd, J = 8.2, 13.6 Hz, 1H), 5.24 (dd, J = 5.5, 7.9 Hz, 1H), 7.26-7.38 (m, 5H), 8.40 (br s, 1H)

AP-MS (m/z): 547 ($\text{M}^+ + 1$)

Example 115 (Compound 122)

[0176] Compound 121 (315 mg, 0.575 mmol) prepared in Example 114 was dissolved in N,N-diethylformamide (9.5 mL). To the solution was added sodium azide (187 mg, 2.88 mmol), and the mixture was stirred at 80°C for 2 hours. To the reaction mixture was added water and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by preparative thin layer chromatography (hexane/

ethyl acetate = 1/2) to obtain Compound 122 (211 mg, yield 72%).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.32 (s, 9H), 1.42 (m, 2H), 1.55-1.74 (m, 4H), 2.35 (t, J = 7.3 Hz, 2H), 2.97 (s, 3H), 3.28 (t, J = 6.7 Hz, 2H), 4.13 (dd, J = 7.2, 14.3 Hz, 1H), 4.63 (dd, J = 8.3, 13.5 Hz, 1H), 5.21 (dd, J = 5.2, 8.0 Hz, 1H), 7.26-7.38 (m, 5H), 8.37 (s, 1H)

5 AP-MS (m/z): 510 (M⁺+1)

Example 116 (Compound 123)

10 [0177] Compound 122 (23.6 mg, 0.0463 mmol) prepared in Example 115 was dissolved in tetrahydrofuran (1.0 mL). To the solution was added triphenylphosphine (36.4 mg, 0.139 mmol), and the mixture was stirred at room temperature for 25 minutes. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by preparative thin layer chromatography (chloroform/methanol/ammonia = 5/0.8/0.2) to obtain Compound 123 (7.1 mg, yield 32%).

15 ¹H-NMR (270 MHz, CDCl₃) δ (ppm): 1.31 (s, 9H), 1.47 (m, 2H), 1.57 (m, 2H), 1.70 (m, 2H), 2.39 (m, 2H), 2.82 (m, 2H), 2.97 (s, 3H), 3.95 (d, J = 13.7 Hz, 1H), 4.14 (br s, 3H), 4.65 (d, J = 13.5 Hz, 1H), 7.24-7.35 (m, 5H)

AP-MS (m/z): 484 (M⁺+1)

Example 117 (Compound 124)

20 [0178] Compound 123 (5.0 mg, 0.010 mmol) prepared in Example 116 was dissolved in dichloromethane (0.4 mL). To the solution was added pyridine (0.0025 mL, 0.031 mmol) and acetyl chloride (0.0015 mL, 0.021 mmol), and the mixture was stirred at room temperature for 0.8 hour. To the reaction mixture was added water and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by preparative thin layer chromatography (chloroform/methanol = 20/1) to obtain Compound 124 (3.9 mg, yield 72%).

25 ¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.32 (s, 9H), 1.37 (m, 2H), 1.53 (m, 2H), 1.69 (m, 2H), 1.98 (s, 3H), 2.39 (t, J = 7.4 Hz, 2H), 2.97 (s, 3H), 3.24 (m, 2H), 3.98 (dd, J = 5.2, 13.6 Hz, 1H), 4.64 (dd, J = 8.2, 13.5 Hz, 1H), 5.22 (dd, J = 5.4, 8.2 Hz, 1H), 5.68 (m, 1H), 7.24-7.38 (m, 5H), 9.08 (s, 1H)

30 FAB-MS (m/z): 526 (M⁺+1)

Example 118 (Compound 125)

[0179]

35

Step 1: In a manner similar to that in Step 1 of Example 1, 3'-hydroxyacetophenone=4-ethylthiosemicarbazone (342 mg, 70%) was obtained from 3'-hydroxyacetophenone (279 mg, 2.05 mmol) and 4-ethylthiosemicarbazide (242 mg, 2.03 mmol).

40 Step 2: In a manner similar to that in Step 2 of Example 1, Compound 125 (90 mg, 60%) was obtained from 3'-hydroxyacetophenone=4-ethylthiosemicarbazone (200 mg, 0.843 mmol) prepared above, acetic anhydride (260 mg, 2.53 mmol) and pyridine (108 μL, 1.34 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.02 (s, 3H), 2.20 (s, 3H), 2.28 (s, 3H), 2.30 (t, J = 8.4 Hz, 3H), 2.36 (s, 3H), 3.30-3.47 (br s, 2H), 7.20-7.40 (m, 5H)

45 Example 119 (Compound 126)

[0180] In a manner similar to that in Example 65, Compound 126 (81 mg, 49%) was obtained from Compound 125 (187 mg, 0.515 mmol) prepared in Example 118, methanol (10 mL) and potassium carbonate (1.00 g, 7.24 mmol).

50 ¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 2.01 (s, 3H), 2.18 (s, 3H), 2.23 (s, 3H), 2.29 (t, J = 8.4 Hz, 3H), 3.40 (br s, 2H), 6.65-6.80 (m, 3H), 7.13 (m, 1H), 11.6 (br s, 1H)

Example 120 (Compound 127)

55 [0181] Compound 69 (50.5 mg, 0.172 mmol) prepared in Example 68 was dissolved in dichloromethane (0.5 mL). To the solution was added triethylamine (17.4 mg, 0.172 mmol) and ethyl isocyanate (13.6 μL, 0.172 mmol), and the mixture was stirred at room temperature for 12 hours. To the reaction mixture was added 1 mol/L hydrochloric acid and water, and the mixture was subjected to separation. The organic layer was washed with saturated aqueous sodium chloride and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the res-

idue was purified by preparative thin layer chromatography (chloroform/methanol/water = 90/10/1) to obtain Compound 127 (53.3 mg, 85%).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.21 (t, J = 7.0 Hz, 3H), 2.09 (s, 3H), 2.22 (s, 3H), 2.35 (s, 3H), 3.31 (m, 2H), 5.03 (br s, 1H), 7.06 (br d, J = 8.4 Hz, 1H), 7.24-7.35 (m, 3H), 8.41 (br s, 1H)

Example 121 (Compound 128)

[0182] In a manner similar to that in Step 3 of Example 76, Compound 128 (500 mg, 63%) was obtained from 3'-hydroxyacetophenone=thiosemicarbazone (398 mg, 1.90 mmol) prepared in Step 1 of Example 59, isobutyryl chloride (1.56 mL, 7.60 mmol) and pyridine (721 mg, 9.12 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.09 (d, J = 6.8 Hz, 3H), 1.10 (d, J = 6.8 Hz, 3H), 1.21 (d, J = 6.8 Hz, 3H), 1.22 (d, J = 6.8 Hz, 3H), 1.29 (d, J = 7.3 Hz, 6H), 2.34 (s, 3H), 2.51 (m, 1H), 2.78 (m, 1H), 3.18 (m, 1H), 7.00 (br d, J = 7.3 Hz, 1H), 7.13 (br s, 1H), 7.25-7.33 (m, 2H), 7.93 (br s, 1H)

Example 122 (Compound 129)

[0183] In a manner similar to that in Example 65, Compound 129 (298 mg, 85%) was obtained from Compound 128 (420 mg, 1.00 mmol) prepared in Example 121 and potassium carbonate (1.00 g, 7.24 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.11 (d, J = 7.0 Hz, 3H), 1.12 (d, J = 7.0 Hz, 3H), 1.22 (d, J = 7.0 Hz, 3H), 1.23 (d, J = 7.0 Hz, 3H), 2.23 (s, 3H), 2.51 (m, 1H), 3.20 (m, 1H), 5.60 (br s, 1H), 6.63 (br d, J = 7.3 Hz, 1H), 6.85 (br s, 1H), 6.94 (br d, J = 7.9 Hz, 1H), 7.15 (br t, J = 7.9 Hz, 1H), 8.00 (br s, 1H)

Example 123 (Compound 130)

[0184] In a manner similar to that in Step 3 of Example 76, Compound 130 (389 mg, 88%) was obtained from 2'-chloroacetophenone=thiosemicarbazone (253 mg, 1.11 mmol) prepared in Step 1 of Example 53, pivaloyl chloride (546 μL, 4.44 mmol) and pyridine (389 μL, 4.80 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.29 (s, 9H), 1.30 (s, 9H), 2.35 (s, 3H), 7.20-7.27 (m, 2H), 7.35-7.43 (m, 2H), 7.95 (br s, 1H)

Example 124 (Compound 131)

[0185] In a manner similar to that in Step 3 of Example 76, Compound 131 (389 mg, 86%) was obtained from 2'-chloroacetophenone=thiosemicarbazone (400 mg, 1.89 mmol) prepared in Step 1 of Example 53, isobutyryl chloride (594 μL, 5.67 mmol) and pyridine (538 mg, 6.80 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.10 (d, J = 6.6 Hz, 3H), 1.12 (d, J = 6.6 Hz, 3H), 1.23 (d, J = 6.9 Hz, 2H), 1.25 (d, J = 6.9 Hz, 3H), 2.39 (s, 3H), 2.52 (m, 1H), 3.18 (m, 1H), 7.22-7.28 (m, 2H), 7.37-7.45 (m, 2H), 7.96 (br s, 1H)

Example 125 (Compound 132)

[0186]

Step 1: In a manner similar to that in Step 1 of Example 1, 1-(5-bromo-2-thienyl)ethanone=thiosemicarbazone (7.33 mg, 86%) was obtained from 1-(5-bromo-2-thienyl)ethanone (630 mg, 3.07 mmol) and thiosemicarbazide (281 mg, 3.07 mmol).

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 132 (158 mg, 58%) was obtained from 1-(5-bromo-2-thienyl)ethanone=thiosemicarbazone (2.11 mg, 0.758 mmol) prepared above and acetic anhydride (10 mL).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.15 (s, 3H), 2.19 (s, 3H), 2.36 (s, 3H), 6.84 (br s, 1H), 6.86 (br s, 1H), 8.29 (br s, 1H)

Example 126 (Compound 133)

[0187]

Step 1: In a manner similar to that in Step 1 of Example 1, 1-(3-bromo-2-thienyl)ethanone=thiosemicarbazone was obtained from 1-(3-bromo-2-thienyl)ethanone (108 mg, 0.388 mmol) and thiosemicarbazide (36.5 mg, 0.399 mmol).

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 133 (139 mg, 99%) was obtained from 1-(3-bromo-2-thienyl)ethanone=thiosemicarbazone prepared above and acetic anhydride (10 mL).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.04 (s, 3H), 2.14 (s, 3H), 2.23 (s, 3H), 2.41 (s, 3H), 6.96 (br s, 1H), 7.17 (br s, 1H), 9.08 (br s, 1H)

Example 127 (Compound 134)

[0188]

Step 1: In a manner similar to that in Step 1 of Example 1, 1-(3-chloro-2-thienyl)ethanone=thiosemicarbazone was obtained from 1-(3-chloro-2-thienyl)ethanone (137 mg, 0.853 mmol) and thiosemicarbazide (78 mg, 0.853 mmol).

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 134 (158 mg, 58%) was obtained from 1-(3-chloro-2-thienyl)ethanone=thiosemicarbazone prepared above and acetic anhydride (10 mL).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.14 (s, 3H), 2.21 (s, 3H), 2.43 (s, 3H), 6.89 (d, J = 5.3 Hz, 1H), 7.18 (d, J = 5.3 Hz, 1H), 8.28 (br s, 1H)

Example 128 (Compound 135)

[0189]

Step 1: In a manner similar to that in Step 1 of Example 1, 1-(3-chloro-2-thienyl)ethanone=thiosemicarbazone (96.1 mg, 71%) was obtained from 1-(3-chloro-2-thienyl)ethanone (92.9 mg, 0.578 mmol) and thiosemicarbazide (52.9 mg, 0.578 mmol).

Step 2: In a manner similar to that in Step 3 of Example 76, Compound 134 (90 mg, 60%) was obtained from 1-(3-chloro-2-thienyl)ethanone=thiosemicarbazone (86.9 mg, 0.372 mmol) prepared above, pivaloyl chloride (138 μL, 1.12 mmol) and pyridine (108 μL, 1.34 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.33 (s, 9H), 1.35 (s, 9H), 2.43 (s, 3H), 6.90 (d, J = 6.3 Hz, 1H), 7.20 (d, J = 6.3 Hz, 1H), 7.97 (br s, 1H)

Example 129 (Compound 136)

[0190] Compound 14 (41 mg, 0.17 mmol) prepared in Example 11 was dissolved in acetonitrile (0.5 mL). To the solution was added di-tert-butyl dicarbonate (0.114 mg, 0.522 mmol) and DMAP (43 mg, 0.35 mmol), and the mixture was stirred at room temperature for 1 hour. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography (chloroform/methanol = 20/1) to obtain Compound 136 (24 mg, 41%).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.47 (s, 9H), 2.21 (s, 3H), 2.40 (s, 3H), 7.14-7.48 (m, 6H)

AP-MS (m/z): 334 (M⁺-1)

Example 130 (Compound 137)

[0191] Compound 14 (74 mg, 0.31 mmol) prepared in Example 11 was dissolved in N,N-dimethylformamide (2 mL). To the solution was added 60% sodium hydride (50 mg, 1.3 mmol) and dimethylcarbamoyl chloride (0.116 mL, 1.26 mmol), and the mixture was stirred at room temperature for 1 hour. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography (chloroform/methanol = 40/1, then ethyl acetate/n-hexane = 3/1) to obtain Compound 137 (44 mg, 46%).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.23 (s, 3H), 2.37 (s, 3H), 3.00 (s, 6H), 7.20-7.45 (m, 5H)

AP-MS (m/z): 307 (M⁺+1)

Example 131 (Compound 138)

[0192]

Step 1: Copper (II) bromide (130 mg, 0.583 mmol) was dissolved in acetonitrile (5.4 mL). To the solution was added tert-butyl nitrite (0.093 mL, 0.78 mmol) under ice cooling. After being stirred for 10 minutes, to the mixture was

added Compound 14 (180 mg, 0.486 mmol) prepared in Example 11, and the mixture was stirred for 1 hour with gradually raising the temperature up to room temperature. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/18) to obtain 3-acetyl-5-bromo-2-methyl-2-phenyl-1,3,4-thiadiazine (145 mg, 84%). Step 2: 3-Acetyl-5-bromo-2-methyl-2-phenyl-1,3,4-thiadiazine (50 mg, 0.17 mmol) prepared above was dissolved in dichloromethane (0.5 mL). To the solution was added piperidine (0.033 mL, 0.33 mmol), and the mixture was stirred at room temperature for 20 minutes. To the reaction mixture was further added piperidine (0.165 mL, 1.67 mmol), and the mixture was stirred at the same temperature for 5.5 hours. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography (chloroform) to obtain Compound 138 (12 mg, 24%).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.60 (m, 6H), 2.25 (s, 3H), 2.40 (s, 3H), 3.24 (m, 4H), 7.20-7.39 (m, 3H), 7.45 (m, 2H)

AP-MS (m/z): 304 (M⁺+1)

Example 132 (Compound 139)

[0193] In a manner similar to that in Step 2 of Example 131, Compound 139 (38 mg, 59%) was obtained from 3-acetyl-5-bromo-2-methyl-2-phenyl-1,3,4-thiadiazine (61 mg, 0.20 mmol) prepared in Step 1 of Example 131 and 4-methylpiperidine (0.483 mL, 4.08 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 0.96 (d, J = 6.4 Hz, 3H), 1.25 (m, 2H), 1.44-1.71 (m, 3H), 2.25 (s, 3H), 2.40 (s, 3H), 2.88 (m, 2H), 3.61 (m, 2H), 7.20-7.49 (m, 3H), 7.46 (m, 2H)

AP-MS (m/z): 318 (M⁺+1)

Example 133 (Compound 140)

[0194] Compound 118 (50 mg, 0.15 mmol) prepared in Example 111 was dissolved in dichloromethane (2 mL). To the solution was added pyridine (0.031 mL, 0.38 mmol) and hexanoyl chloride (0.053 mL, 0.38 mmol), and the mixture was stirred at room temperature for 2.5 hours. To the reaction mixture was further added pyridine (0.012 mL, 0.15 mmol) and hexanoyl chloride (0.021 mL, 0.15 mmol), and the mixture was stirred at the same temperature for 1 hour. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography (chloroform/methanol = 15/1) to obtain Compound 140 (52 mg, 80%).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 0.90 (t, J = 6.6 Hz, 3H), 1.22-1.41 (m, 4H), 1.64 (m, 2H), 2.31 (s, 3H), 2.32 (t, J = 7.5 Hz, 2H), 2.96 (s, 3H), 3.98 (dd, J = 5.4, 13.9 Hz, 1H), 4.60 (dd, J = 8.1, 13.9 Hz, 1H), 5.38 (dd, J = 5.4, 8.1 Hz, 1H), 7.20-7.44 (m, 5H), 8.02 (s, 1H)

AP-MS (m/z): 427 (M⁺+1)

Example 134 (Compound 141)

[0195] In a manner similar to that in Example 133, Compound 141 (22 mg, 18%) was obtained from Compound 118 (100 mg, 0.305 mmol) prepared in Example 111, pyridine (0.062 mL, 0.78 mmol) and crotonoyl chloride (0.075 mL, 0.78 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.91 (dd, J = 1.7, 7.0 Hz, 3H), 2.32 (s, 3H), 2.97 (s, 3H), 3.99 (dd, J = 5.6, 13.9 Hz, 1H), 4.61 (dd, J = 7.6, 13.9 Hz, 1H), 5.51 (dd, J = 5.6, 7.6 Hz, 1H), 5.86 (dd, J = 1.7, 15.2 Hz, 1H), 7.03 (dd, J = 7.0, 15.2 Hz, 1H), 7.22-7.41 (m, 5H), 8.49 (s, 1H)

AP-MS (m/z): 397 (M⁺+1)

Example 135 (Compound 142)

[0196] In a manner similar to that in Example 133, Compound 142 (42 mg, 70%) was obtained from Compound 118 (50 mg, 0.15 mmol) prepared in Example 111, pyridine (0.062 mL, 0.78 mmol) and cyclopropanecarbonyl chloride (0.070 mL, 0.76 mmol).

¹H NMR (270 MHz, CD₃OD) δ (ppm): 0.87-0.98 (m, 4H), 1.77 (m, 1H), 2.28 (s, 3H), 3.01 (s, 3H), 3.97 (d, J = 14.0 Hz, 1H), 4.55 (d, J = 14.0 Hz, 1H), 7.22-7.42 (m, 5H)

AP-MS (m/z): 397 ($M^+ + 1$)

Example 136 (Compound 143)

- 5 [0197] In a manner similar to that in Example 133, Compound 143 (24 mg, 22%) was obtained from Compound 118 (80 mg, 0.24 mmol) prepared in Example 111, pyridine (0.069 mL, 0.85 mmol) and 2-acetoxyisobutyl chloride (0.12 mL, 0.85 mmol).
 ^1H NMR (270 MHz, CDCl_3) δ (ppm): 1.65 (s, 3H), 1.67 (s, 3H), 2.15 (s, 3H), 2.32 (s, 3H), 2.97 (s, 3H), 3.99 (dd, J = 5.5, 14.0 Hz, 1H), 4.61 (dd, J = 8.1, 14.0 Hz, 1H), 5.39 (dd, J = 5.5, 8.1 Hz, 1H), 7.29-7.46 (m, 5H), 8.53 (s, 1H)
 10 AP-MS (m/z): 457 ($M^+ + 1$)

Example 137 (Compound 144)

- 15 [0198] Compound 143 (21 mg, 0.045 mmol) prepared in Example 136 was dissolved in a mixed solvent of methanol (1.6 mL) and water (0.8 mL). To the solution was added lithium hydroxide (11 mg, 0.45 mmol), and the mixture was stirred at room temperature for 3.5 hours. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography (chloroform/methanol = 9/1) to obtain Compound 144 (11 mg, 56%).
 20 ^1H NMR (270 MHz, CDCl_3) δ (ppm): 1.44 (s, 3H), 1.48 (s, 3H), 2.32 (s, 3H), 2.85 (br s, 1H), 2.97 (s, 3H), 3.98 (dd, J = 5.6, 13.9 Hz, 1H), 4.63 (dd, J = 7.8, 13.9 Hz, 1H), 5.53 (dd, J = 5.6, 7.8 Hz, 1H), 7.25-7.42 (m, 5H), 9.36 (s, 1H)
 AP-MS (m/z): 415 ($M^+ + 1$)

Example 138 (Compound 145)

- 25 [0199] In a manner similar to that in Example 133, Compound 145 (53 mg, 86%) was obtained from Compound 118 (50 mg, 0.15 mmol) prepared in Example 111, pyridine (0.031 mL, 0.38 mmol) and methoxyacetyl chloride (0.035 mL, 0.38 mmol).
 ^1H NMR (270 MHz, CDCl_3) δ (ppm): 2.32 (s, 3H), 2.96 (s, 3H), 3.49 (s, 3H), 4.00 (s, 2H), 4.00 (dd, J = 5.8, 13.9 Hz, 1H), 4.61 (dd, J = 7.8, 13.9 Hz, 1H), 5.46 (dd, J = 5.8, 7.8 Hz, 1H), 7.25-7.44 (m, 5H), 8.94 (s, 1H)
 30 AP-MS (m/z): 401 ($M^+ + 1$)

Example 139 (Compound 146)

- 35 [0200] In a manner similar to that in Example 133, Compound 146 (105 mg, 85%) was obtained from Compound 118 (100 mg, 0.305 mmol) prepared in Example 111, pyridine (0.062 mL, 0.76 mmol) and chloroacetyl chloride (0.081 mL, 0.76 mmol).
 ^1H NMR (270 MHz, CDCl_3) δ (ppm): 2.34 (s, 3H), 2.97 (s, 3H), 4.02 (dd, J = 5.6, 14.0 Hz, 1H), 4.11 (d, J = 15.9 Hz, 1H), 4.18 (d, J = 15.9 Hz, 1H), 4.62 (dd, J = 7.8, 14.0 Hz, 1H), 5.28 (dd, J = 5.6, 7.8 Hz, 1H), 7.22-7.43 (m, 5H), 8.87 (s, 1H)
 40 AP-MS (m/z): 405 ($M^+ + 1$)

Example 140 (Compound 147)

- 45 [0201] Compound 146 (50 mg, 0.12 mmol) prepared in Example 139 was dissolved in methanol (1 mL). To the solution was added 50% aqueous dimethylamine (0.033 mL), and the mixture was stirred at room temperature for 1 hour. To the reaction mixture was further added 50% aqueous dimethylamine (0.033 mL), and the mixture was stirred at the same temperature for 1.5 hours. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography (chloroform/acetone = 1/1) to obtain Compound 147 (20 mg, 39%).
 50 ^1H NMR (270 MHz, CDCl_3) δ (ppm): 2.34 (s, 3H), 2.38 (s, 6H), 2.96 (s, 3H), 3.06 (d, J = 17.3 Hz, 1H), 3.10 (d, J = 17.3 Hz, 1H), 4.00 (d, J = 13.9 Hz, 1H), 4.61 (d, J = 13.9 Hz, 1H), 5.36 (br, 1H), 7.25-7.41 (m, 5H)
 AP-MS (m/z): 414 ($M^+ + 1$)
 55

Example 141 (Compound 148)

- [0202] In a manner similar to that in Example 133, Compound 148 (304 mg, 74%) was obtained from Compound

118 (297 mg, 0.903 mmol) prepared in Example 111, pyridine (0.183 mL, 2.26 mmol) and methyl 4-(chloroformyl) butyrate (0.312 mL, 2.26 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.00 (m, 2H), 2.32-2.56 (m, 4H), 2.34 (s, 3H), 2.99 (s, 3H), 3.71 (s, 3H), 4.01 (dd, J = 5.4, 13.9 Hz, 1H), 4.63 (dd, J = 7.9, 13.9 Hz, 1H), 5.45 (m, 1H), 7.21-7.49 (m, 5H), 8.54 (s, 1H)

AP-MS (m/z): 457 (M⁺+1)

Example 142 (Compound 149)

[0203] In a manner similar to that in Example 137, after Compound 148 (262 mg, 0.573 mmol) prepared in Example 141 was treated with lithium hydroxide monohydrate (206 mg, 4.91 mmol), to the reaction mixture was added ice and 0.5 mol/L hydrochloric acid, and the mixture was extracted with a mixed solvent of chloroform and methanol. After the extract was concentrated, the residue was purified by silica gel column chromatography (chloroform/methanol = 43/7) to obtain Compound 149 (222 mg, 88%).

¹H NMR (270 MHz, CD₃OD) δ (ppm): 1.89 (m, 2H), 2.28 (s, 3H), 2.33 (t, J = 7.3 Hz, 2H), 2.43 (t, J = 7.5 Hz, 2H), 3.01 (s, 3H), 3.99 (d, J = 14.0 Hz, 1H), 4.56 (d, J = 14.0 Hz, 1H), 7.20-7.45 (m, 5H)

AP-MS (m/z): 441 (M⁻-1)

Example 143 (Compound 150)

[0204] Compound 149 (83 mg, 0.19 mmol) prepared in Example 142 was dissolved in 1,2-dichloroethane (3.2 mL). To the solution was added thionyl chloride (3.2 mL), and the mixture was stirred at 60°C for 2.5 hours. The reaction mixture was concentrated under reduced pressure, and then the residue was purified by preparative thin layer chromatography (chloroform/methanol = 20/1) to obtain Compound 150 (61 mg, 76%). ¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.09 (m, 2H), 2.29 (s, 3H), 2.80 (t, J = 6.5 Hz, 4H), 3.05 (s, 3H), 3.95 (dd, J = 3.7, 13.9 Hz, 1H), 4.82 (dd, J = 9.6, 13.9 Hz, 1H), 5.70 (dd, J = 3.7, 9.6 Hz, 1H), 7.29-7.47 (m, 3H), 7.58 (m, 2H)

AP-MS (m/z): 425 (M⁺+1)

Example 144 (Compound 151)

[0205] In a manner similar to that in Example 133, Compound 151 (113 mg, 78%) was obtained from Compound 118 (100 mg, 0.305 mmol) prepared in Example 111, pyridine (0.062 mL, 0.76 mmol) and 4-bromobutyl chloride (0.088 mL, 0.76 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.20 (m, 2H), 2.31 (s, 3H), 2.55 (t, J = 6.9 Hz, 2H), 2.96 (s, 3H), 3.47 (t, J = 6.2 Hz, 2H), 3.99 (dd, J = 5.5, 13.9 Hz, 1H), 4.61 (dd, J = 7.9, 13.9 Hz, 1H), 5.37 (dd, J = 5.5, 7.9 Hz, 1H), 7.23-7.42 (m, 5H), 8.18 (s, 1H)

AP-MS (m/z): 476 (M⁻-1)

Example 145 (Compound 152)

[0206] Compound 151 (70 mg, 0.15 mmol) prepared in Example 144 was dissolved in N,N-dimethylformamide (1.8 mL). To the solution was added 60% sodium hydride (9 mg, 0.2 mmol), and the mixture was stirred at room temperature for 2 hours. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography (chloroform/methanol = 9/1) to obtain Compound 152 (51 mg, 88%).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.20 (m, 2H), 2.35 (s, 3H), 2.57 (m, 2H), 2.95 (s, 3H), 3.93 (m, 2H), 3.99 (dd, J = 5.5, 13.9 Hz, 1H), 4.61 (dd, J = 8.1, 13.9 Hz, 1H), 5.33 (dd, J = 5.5, 8.1 Hz, 1H), 7.25-7.44 (m, 5H)

AP-MS (m/z): 397 (M⁺+1)

Example 146 (Compound 153)

[0207] In a manner similar to that in Example 133, Compound 153 (120 mg, 80%) was obtained from Compound 118 (100 mg, 0.305 mmol) prepared in Example 111, pyridine (0.087 mL, 1.1 mmol) and 5-bromovaleryl chloride (0.143 mL, 1.07 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.75-1.98 (m, 4H), 2.31 (s, 3H), 2.36 (t, J = 7.0 Hz, 2H), 2.96 (s, 3H), 3.40 (t, J = 6.2 Hz, 2H), 3.99 (dd, J = 5.5, 13.9 Hz, 1H), 4.61 (dd, J = 7.9, 13.9 Hz, 1H), 5.40 (dd, J = 5.5, 7.9 Hz, 1H), 7.23-7.42 (m, 5H), 8.22 (s, 1H)

AP-MS (m/z): 491, 493 (M⁺+1)

Example 147 (Compound 154)

[0208] In a manner similar to that in Example 145, Compound 154 (36 mg, 72%) was obtained from Compound 153 (60 mg, 0.12 mmol) prepared in Example 148 and 60% sodium hydride (7 mg, 0.2 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.81-2.02 (m, 4H), 2.36 (s, 3H), 2.54 (m, 2H), 2.94 (s, 3H), 3.85 (m, 2H), 3.95 (dd, J = 4.8, 13.8 Hz, 1H), 4.56 (dd, J = 8.4, 13.8 Hz, 1H), 5.41 (dd, J = 4.8, 8.4 Hz, 1H), 7.25-7.41 (m, 5H)

AP-MS (m/z): 411 (M⁺+1)

Example 148 (Compound 155)

[0209] In a manner similar to that in Example 133, Compound 155 (122 mg, 80%) was obtained from Compound 118 (99 mg, 0.30 mmol) prepared in Example 111, pyridine (0.061 mL, 0.75 mmol) and 6-bromohexanoyl chloride (0.115 mL, 0.754 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.40-1.77 (m, 4H), 1.87 (m, 2H), 2.31 (s, 3H), 2.35 (t, J = 7.4 Hz, 2H), 2.96 (s, 3H), 3.40 (t, J = 6.6 Hz, 2H), 3.99 (dd, J = 5.4, 14.0 Hz, 1H), 4.60 (dd, J = 7.9, 14.0 Hz, 1H), 5.36 (dd, J = 5.4, 7.9 Hz, 1H), 7.20-7.43 (m, 5H), 8.06 (s, 1H)

AP-MS (m/z): 505, 507 (M⁺+1)

Example 149 (Compound 156)

[0210] In a manner similar to that in Example 145, Compound 156 (17 mg, 32%) was obtained from Compound 155 (63 mg, 0.12 mmol) prepared in Example 148 and 60% sodium hydride (7 mg, 0.2 mmol).

¹H NMR (270 MHz, DMSO-d₆) δ (ppm): 1.55-1.78 (m, 6H), 2.19 (s, 3H), 2.68 (m, 2H), 2.95 (s, 3H), 3.87 (dd, J = 7.9, 13.7 Hz, 1H), 4.12 (m, 2H), 4.29 (dd, J = 5.6, 13.7 Hz, 1H), 7.20-7.41 (m, 6H)

AP-MS (m/z): 425 (M⁺+1)

Example 150 (Compound 157)

[0211] Compound 99 (1.50 g, 3.21 mmol) prepared in Example 92 was dissolved in methanol (30 mL). To the solution was gradually added sodium borohydride (1.21 g, 32.0 mmol) at 50°C, and the mixture was stirred at the same temperature for 1.5 hours. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol = 20/1) to obtain Compound 157 (0.26 g, 21%).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.31 (s, 9H), 2.62 (m, 1H), 2.94 (s, 3H), 3.22 (m, 1H), 3.41 (m, 1H), 3.61 (m, 1H), 4.21 (s, 2H), 4.79 (m, 1H), 7.19-7.38 (m, 5H)

AP-MS (m/z): 385 (M⁺+1)

Example 151 (Compound 158)

[0212] In a manner similar to that in Example 133, Compound 158 (114 mg, 85%) was obtained from Compound 157 (97 mg, 0.25 mmol) prepared in Example 150, pyridine (0.051 mL, 0.63 mmol) and 4-bromobutyl chloride (0.073 mL, 0.63 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.32 (s, 9H), 2.22 (m, 2H), 2.58 (t, J = 7.4 Hz, 2H), 2.65 (m, 1H), 2.97 (s, 3H), 3.27 (m, 1H), 3.39 (m, 1H), 3.49 (t, J = 6.2 Hz, 2H), 3.62 (m, 1H), 4.45 (br t, 1H), 7.21-7.39 (m, 5H), 8.00 (s, 1H)

AP-MS (m/z): 533, 535 (M⁺+1)

Example 152 (Compound 159)

[0213] In a manner similar to that in Example 145, Compound 159 (64 mg, 68%) was obtained from Compound 158 (110 mg, 0.206 mmol) prepared in Example 151 and 60% sodium hydride (12 mg, 0.31 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.34 (s, 9H), 2.23 (m, 2H), 2.56 (m, 2H), 2.61 (m, 1H), 2.97 (s, 3H), 3.27 (m, 1H), 3.40 (m, 1H), 3.63 (m, 1H), 3.98 (m, 2H), 4.01 (br t, J = 3.5 Hz, 1H), 7.20-7.37 (m, 5H)

AP-MS (m/z): 453 (M⁺+1)

Example 153 (Compound 160)

[0214] Compound 119 (21 mg, 0.052 mmol) prepared in Example 112 was dissolved in a mixed solvent of toluene

(1 mL) and tetrahydrofuran (1 mL). To the solution was added 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphethane-2,4-disulfide (Lawesson's reagent) (43 mg, 0.11 mmol), and the mixture was stirred at 90°C for 5 hours. The reaction mixture was purified by preparative thin layer chromatography (chloroform/methanol = 20/1) to obtain Compound 160 (15 mg, 67%).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.30 (s, 9H), 2.76 (s, 3H), 3.08 (s, 3H), 4.08 (dd, J = 7.3, 13.8 Hz, 1H), 5.03 (t, J = 7.3 Hz, 1H), 5.54 (dd, J = 7.3, 13.8 Hz, 1H), 7.26-7.42 (m, 5H), 8.16 (s, 1H)

AP-MS (m/z): 429 (M⁺+1)

Example 154 (Compound 161)

[0215] In a manner similar to that in Example 100, Compound 161 (70 mg, 37%) was obtained from Compound 106 (0.165 g, 0.393 mmol) prepared in Example 99, oxalyl chloride (2 mL), 2-(methylamino)ethanol (295 mg, 3.93 mmol) and triethylamine (476 mg, 4.72 mmol).

AP-MS (m/z): 475 (M⁺-1)

Example 155 (Compound 162)

[0216] In a manner similar to that in Example 100, Compound 162 (135 mg, 68%) was obtained from Compound 106 (0.165 g, 0.393 mmol) prepared in Example 99, oxalyl chloride (2 mL) and diethanolamine (413 mg, 3.93 mmol).

AP-MS (m/z): 507 (M⁺+1)

Example 156 (Compounds 163 and 164)

[0217] In a manner similar to that in Example 100, Compound 163 (6.2 mg, 5%) and Compound 164 (36.1 mg, 31%) were obtained from Compound 106 (0.099 g, 0.237 mmol) prepared in Example 99, oxalyl chloride (1.25 mL) and 3-amino-1,2-propanediol (92 μL, 1.19 mmol).

Compound 163

[0218] AP-MS (m/z): 493 (M⁺+1)

Compound 164

[0219] AP-MS (m/z): 493 (M⁺+1)

Example 157 (Compound 165)

[0220] In a manner similar to that in Example 100, Compound 165 (37 mg, 33%) was obtained from Compound 115 (0.102 g, 0.236 mmol) prepared in Example 108, oxalyl chloride (1.25 mL) and 2-aminoethanol (144 mg, 2.36 mmol).

AP-MS (m/z): 477 (M⁺+1)

Example 158 (Compound 166)

[0221] Compound 105 (0.200 g, 0.461 mmol) prepared in Example 98 was dissolved in tetrahydrofuran (2 mL). To the solution was added lithium aluminium hydride (30 mg, 0.791 mmol) at 0°C, and the mixture was stirred at room temperature for 2 hours. To the reaction mixture was added water and 30% aqueous sodium hydroxide. The insoluble precipitate was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by preparative thin layer chromatography (chloroform/methanol = 9/1) to obtain Compound 166 (64.0 mg, 34%). ¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.29 (s, 9H), 1.32 (s, 9H), 1.65 (m, 1H), 2.08 (m, 1H), 2.33 (m, 1H), 3.16 (m, 1H), 3.78 (m, 2H), 7.21-7.38 (m, 5H), 7.95 (br s, 1H)

AP-MS (m/z): 404 (M⁺-1)

Example 159 (Compound 167)

[0222] Compound 166 (0.0448 g, 0.110 mmol) prepared in Example 158 was dissolved in N,N-dimethylacetamide (0.5 mL). To the solution was added sulfamoyl chloride (51.1 mg, 0.442 mmol) at 0°C with stirring, and the mixture was stirred at 0°C for 20 minutes. After to the reaction mixture was added water, and the mixture was stirred. The deposited solid was collected by filtration, and dried under reduced pressure. The resulting solid was purified by preparative thin

layer chromatography (chloroform/methanol = 30/1) to obtain Compound 167 (30.2 mg, 57%).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.29 (s, 9H), 1.33 (s, 9H), 1.89 (m, 1H), 2.14 (m, 1H), 2.38 (m, 1H), 3.32 (m, 1H), 4.28 (m, 1H), 4.43 (m, 1H), 5.08 (br s, 1H), 7.29 (m, 5H), 7.93 (br s, 1H)

AP-MS (m/z): 483 (M-1)

Example 160 (Compounds 168 and 169)

[0223]

Step 1: 2-Aminoacetophenone hydrochloride (4.58 g, 28.6 mmol) was dissolved in dichloromethane (250 mL). To the solution was added triethylamine (9.30 mL, 66.7 mmol), and the mixture was stirred at room temperature for 10 minutes. After the reaction mixture was cooled to 0°C, chloromethanesulfonyl chloride (purity 90%, 3.60 mL, 36.3 mmol) was added to the mixture, and the mixture was stirred at the same temperature for 1 hour. To the reaction mixture was added 2 mol/L hydrochloric acid, and the mixture was extracted with chloroform. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. To the residue was added diethyl ether, and the deposited crystals were collected by filtration and dried to obtain 2-(chloromethylsulfonylamino)acetophenone (5.00 g, 76%).

¹H NMR (300 MHz, DMSO-d₆) δ (ppm): 4.67 (s, 2H), 4.94 (s, 2H), 7.54 (t, J = 8.1 Hz, 2H), 7.67 (t, J = 7.5 Hz, 1H), 7.97 (d, J = 8.1 Hz, 2H), 8.01 (br s, 1H)

AP-MS (m/z): 247 (M⁺)

Step 2: 2-(Chloromethylsulfonylamino)acetophenone (1.00 g, 4.05 mmol) prepared above and thiosemicarbazide hydrochloride (1.03 g, 8.07 mmol) were dissolved in methanol (60 mL). To the solution was added concentrated hydrochloric acid (1.00 mL), and the mixture was stirred at 60°C for 2 hours. The reaction mixture was concentrated, and to the residue was added ethyl acetate and saturated aqueous sodium hydrogencarbonate, and the mixture was subjected to separation. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/1 and 2/1) to obtain 2-(chloromethylsulfonylamino)acetophenone=thiosemicarbazone (0.51 g, 40%).

¹H NMR (300 MHz, DMSO-d₆) δ (ppm): 4.17 (s, 2H), 4.93 (s, 2H), 7.37-7.42 (m, 3H), 7.52-7.56 (m, 2H), 8.13 (br s, 1H), 8.48 (br, 2H), 8.85 (br s, 1H)

AP-MS (m/z): 319 (M⁺)

Step 3: 2-(Chloromethylsulfonylamino)acetophenone=thiosemicarbazone (7.48 g, 23.4 mmol) prepared above was dissolved in chloroform (250 mL). To the solution was added pyridine (11.4 mL, 141 mmol) and pivaloyl chloride (8.70 mL, 70.6 mmol), and the mixture was stirred at room temperature for 30 minutes. To the reaction mixture was added acetic anhydride (4.40 mL, 46.6 mmol), and the mixture was further stirred at room temperature for 15 hours. To the reaction mixture was added 2 mol/L hydrochloric acid, and the mixture was extracted with chloroform. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/1 and 2/1) to obtain Compound 168 (3.56 g, 25%) and Compound 169 (1.77 g, 14%).

¹H NMR (300 MHz, DMSO-d₆) δ (ppm): 1.16 (s, 9H), 2.23 (s, 3H), 4.00 (dd, J = 11.3, 8.0 Hz, 1H), 4.47 (dd, J = 11.3, 2.5 Hz, 1H), 4.91 (d, J = 12.0 Hz, 1H), 4.97 (d, J = 12.0 Hz, 1H), 7.28-7.39 (m, 5H), 8.10 (br s, 1H), 11.2 (br s, 1H)

AP-MS (m/z): 446 (M⁺)

Compound 169

[0224] ¹H NMR (300 MHz, DMSO-d₆) δ (ppm): 2.01 (s, 3H), 2.18 (s, 3H), 3.95 (d, J = 14.3 Hz, 1H), 4.45 (d, J = 14.3 Hz, 1H), 4.91 (d, J = 12.0 Hz, 1H), 4.97 (d, J = 12.0 Hz, 1H), 7.25-7.39 (m, 5H), 8.08 (br s, 1H), 11.6 (br s, 1H)

AP-MS (m/z): 404 (M⁺)

Example 161 (Compounds 170 and 171)

[0225]

Step 1: 2-Aminoacetophenone hydrochloride (1.00 g, 5.85 mmol) was dissolved in dichloromethane (50 mL). To the solution was added triethylamine (2.50 mL, 17.9 mmol), and the mixture was stirred at room temperature for 10 minutes. After the reaction mixture was cooled to 0°C, chloroethanesulfonyl chloride (0.92 mL, 8.80 mmol) was

added to the mixture, and the mixture was stirred at the same temperature for 15 minutes. To the reaction mixture was added 2 mol/L hydrochloric acid and the mixture was extracted with chloroform. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. To the residue was added a mixed solvent of ethyl acetate and n-hexane for

crystallization to obtain 2-(vinylsulfonylamino)acetophenone (0.42 g, 32%).
¹H NMR (300 MHz, CDCl₃) δ (ppm): 4.54 (d, J = 4.5 Hz, 2H), 5.42 (br s, 1H), 5.94 (d, J = 9.9 Hz, 1H), 6.28 (d, J = 16.5 Hz, 1H), 6.53 (br dd, J = 16.2, 9.9 Hz, 1H), 7.52 (t, J = 7.5 Hz, 3H), 7.65 (t, J = 7.8 Hz, 1H), 7.93 (t, J = 5.1 Hz, 1H)

AP-MS (m/z): 225 (M⁺)

Step 2: 2-(Vinylsulfonylamino)acetophenone (0.32 g, 1.42 mmol) prepared above and thiosemicarbazide hydrochloride (0.27 g, 2.13 mmol) were dissolved in methanol (20 mL). To the solution was added concentrated hydrochloric acid (2 drops), and the mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated. To the residue was added ethyl acetate and saturated aqueous sodium hydrogencarbonate, and the mixture was subjected to separation. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/1) to obtain 2-(vinylsulfonylamino)acetophenone=thiosemicarbazone (0.25 g, 58%).

¹H NMR (300 MHz, CDCl₃) δ (ppm): 4.10 (s, 2H), 5.97 (d, J = 9.9 Hz, 1H), 6.25 (d, J = 16.8 Hz, 1H), 6.54 (dd, J = 16.8, 9.9 Hz, 1H), 7.24-7.27 (m, 2H), 7.42 (br s, 1H), 7.52-7.53 (m, 3H), 7.81 (br s, 1H), 8.70 (m, 1H)

AP-MS (m/z): 297 (M⁺)

Step 3: 2-(Vinylsulfonylamino)acetophenone=thiosemicarbazone (0.25 g, 0.83 mmol) prepared above was dissolved in acetone (10 mL). To the solution was added pyridine (0.34 mL, 4.17 mmol) and pivaloyl chloride (0.31 mL, 2.50 mmol), and the mixture was stirred at room temperature for 30 minutes. To the reaction mixture was added acetic anhydride (0.16 mL, 1.66 mmol), and the mixture was further stirred for 3 days at room temperature. The reaction mixture was concentrated, and to the residue was added ethyl acetate and 2 mol/L hydrochloric acid, and the mixture was subjected to separation. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/1) to obtain Compound 170 (0.18 g, 52%) and Compound 171 (0.10 g, 26%).

Compound 170

[0226] ¹H NMR (300 MHz, CDCl₃) δ (ppm): 1.27 (s, 9H), 2.31 (s, 3H), 3.87 (dd, J = 13.4, 5.0 Hz, 1H), 4.45 (dd, J = 13.4, 7.9 Hz, 1H), 5.57 (br s, 1H), 5.92 (d, J = 9.9 Hz, 1H), 6.25 (d, J = 16.5 Hz, 1H), 6.49 (dd, J = 16.5, 9.9 Hz, 1H), 7.27-7.34 (m, 5H), 8.22 (br s, 1H)

AP-MS (m/z): 424 (M⁺)

Compound 171

[0227] ¹H NMR (300 MHz, CDCl₃) δ (ppm): 1.29 (s, 9H), 1.33 (s, 9H), 3.85 (dd, J = 13.5, 4.8 Hz, 1H), 4.49 (dd, J = 13.5, 8.1 Hz, 1H), 5.29 (br s, 1H), 5.93 (br d, J = 9.9 Hz, 1H), 6.27 (br d, J = 16.5 Hz, 1H), 6.53 (br dd, J = 16.4, 9.6 Hz, 1H), 7.27-7.34 (m, 5H), 8.06 (br s, 1H) AP-MS (m/z): 466 (M⁺)

Example 162 (Compound 172)

[0228] Compound 170 (0.05 g, 0.11 mmol) prepared in Step 3 of Example 161 was dissolved in acetonitrile (3 mL). To the solution was added morpholine (0.10 mL), and the mixture was stirred at 80°C for 2 hours. The reaction mixture was concentrated, and the residue was purified by silica gel column chromatography (chloroform/methanol = 10/1) to obtain Compound 172 (0.04 g, 77%). ¹H NMR (300 MHz, CDCl₃) δ (ppm): 1.27 (s, 9H), 2.33 (s, 3H), 2.42-2.45 (m, 4H), 2.78 (dquin, J = 16.5, 6.0 Hz, 2H), 3.19 (t, J = 6.6 Hz, 2H), 3.65-3.68 (m, 4H), 4.04 (dd, J = 14.1, 4.8 Hz, 1H), 4.55 (dd, J = 14.1, 7.5 Hz, 1H), 5.73 (br s, 1H), 7.30-7.38 (m, 5H), 8.05 (br s, 1H)

AP-MS (m/z): 511 (M⁺)

Example 163 (Compound 173)

[0229] In a manner similar to that in Example 162, Compound 173 (0.03 g, 66%) was obtained from Compound 170 (0.05 g, 0.11 mmol) prepared in Step 3 of Example 161 and 70% aqueous ethylamine (0.10 mL).

¹H NMR (300 MHz, CDCl₃) δ (ppm): 1.10 (t, J = 6.9 Hz, 3H), 1.27 (s, 9H), 2.32 (s, 3H), 2.65 (quin, J = 7.2 Hz, 2H),

3.05-3.09 (m, 2H), 3.18-3.20 (m, 2H), 4.00 (d, J = 13.5 Hz, 1H), 4.55 (d, J = 13.8 Hz, 1H), 7.30-7.37 (m, 5H), 8.07 (br s, 1H)

AP-MS (m/z): 470 (M⁺+1)

5 Example 164 (Compound 174)

[0230] In a manner similar to that in Example 162, Compound 174 (0.03 g, 67%) was obtained from Compound 170 (0.05 g, 0.11 mmol) prepared in Step 3 of Example 161 and 2 mol/L dimethylamine methanol solution (0.10 mL).

¹H NMR (300 MHz, CDCl₃) δ (ppm): 1.26 (s, 9H), 2.24 (s, 6H), 2.31 (s, 3H), 2.71-2.81 (m, 2H), 3.12-3.19 (m, 2H), 4.00 (d, J = 13.5 Hz, 1H), 4.56 (d, J = 13.5 Hz, 1H), 6.00 (br s, 1H), 7.31-7.36 (m, 5H), 8.06 (br s, 1H)

AP-MS (m/z): 469 (M⁺)

Example 165 (Compound 175)

15 [0231] In a manner similar to that in Example 162, Compound 175 (0.03 g, 52%) was obtained from Compound 170 (0.05 g, 0.11 mmol) prepared in Step 3 of Example 161 and 2-aminoethanol (0.10 mL). ¹H NMR (300 MHz, CDCl₃) δ (ppm): 1.26 (s, 9H), 2.35 (s, 3H), 2.65-2.78 (m, 2H), 3.08-3.30 (m, 4H), 3.64 (t, J = 5.1 Hz, 2H), 3.98 (d, J = 13.5 Hz, 1H), 4.54 (d, J = 13.5 Hz, 1H), 7.26-7.38 (m, 5H), 8.25 (br s, 1H)

AP-MS (m/z): 485 (M⁺)

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Example 166 (Compound 176)

[0232] In a manner similar to that in Example 162, Compound 176 (0.01 g, 26%) was obtained from Compound 171 (0.05 g, 0.11 mmol) prepared in Step 3 of Example 161 and 70% aqueous ethylamine (0.10 mL).

25 ¹H NMR (300 MHz, CDCl₃) δ (ppm): 1.18 (m, 3H), 1.28 (s, 9H), 1.34 (s, 9H), 2.63 (quin, J = 7.0 Hz, 2H), 2.73 (br q, J = 6.3 Hz, 1H), 2.84 (br q, J = 6.2 Hz, 1H), 3.18 (br t, J = 6.6 Hz, 2H), 4.02 (d, J = 13.2 Hz, 1H), 4.58 (d, J = 13.2 Hz, 1H), 5.85 (br s, 1H), 7.27-7.35 (m, 5H), 8.02 (br s, 1H)

AP-MS (m/z): 512 (M⁺+1)

30 Example 167 (Compound 177)

[0233] In a manner similar to that in Example 162, Compound 177 (0.02 g, 39%) was obtained from Compound 171 (0.05 g, 0.11 mmol) prepared in Step 3 of Example 161 and 2 mol/L dimethylamine methanol solution (0.10 mL).

35 ¹H NMR (300 MHz, CDCl₃) δ (ppm): 1.28 (s, 9H), 1.34 (s, 9H), 2.25 (s, 6H), 2.73 (br q, J = 6.3 Hz, 1H), 2.84 (br q, J = 6.2 Hz, 1H), 3.18 (br t, J = 6.6 Hz, 2H), 4.02 (d, J = 13.2 Hz, 1H), 4.58 (d, J = 13.2 Hz, 1H), 5.85 (br s, 1H), 7.27-7.35 (m, 5H), 8.02 (br s, 1H)

AP-MS (m/z): 512 (M⁺+1)

40 Example 168 (Compound 178)

[0234] In a manner similar to that in Example 11, Compound 178 (64.0 mg, 38%) was obtained from carbomethoxypropionophenone=thiosemicarbazone (0.144 g, 0.543 mmol) prepared in Step 1 of Example 98, acetic anhydride (77 μL, 0.814 mmol) and pyridine (79 μL, 0.977 mmol).

45 ¹H NMR (270 MHz, CDCl₃) δ (ppm): 2.13 (s, 3H), 2.20-2.70 (m, 4H), 3.61 (s, 3H), 6.52 (br s, 2H), 7.20-7.35 (m, 5H)

Example 169 (Compound 179)

[0235] In a manner similar to that in Example 15, Compound 179 (24.0 mg, 94%) was obtained from Compound 178 (0.0200 g, 0.0650 mmol) prepared in Example 168, pivaloyl chloride (16 μL, 0.130 mmol) and pyridine (15 μL, 0.182 mmol).

50 ¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.30 (s, 9H), 2.10 (s, 3H), 2.17-2.75 (m, 4H), 3.57 (s, 3H), 7.18-7.32 (m, 5H), 8.02 (br s, 1H)

AP-MS (m/z): 390 (M-1)

55 Example 170 (Compound 180)

[0236] Compound 100 (304 mg, 0.0690 mmol) prepared in Example 93 and cerium chloride heptahydrate (257 mg, 0.690 mmol) were dissolved in methanol (800 mL). To the solution was gradually added sodium borohydride (522 mg,

13.8 mmol), and the mixture was stirred at room temperature for 20 minutes. The reaction mixture was concentrated under reduced pressure. To the residue was added 1 mol/L hydrochloric acid (100 mL), and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/acetone/ethyl acetate/n-hexane = 9/1/1/1) to obtain Compound 180 (217 mg, 85%).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.14 (t, J = 7.0 Hz, 6H), 2.68 (m, 1H), 2.98 (s, 3H), 3.27 (m, 2H), 3.44 (m, 1H), 3.63 (m, 1H), 4.18 (br s, 2H), 4.51 (br s, 1H), 7.30 (m, 5H) AP-MS (m/z): 371 (M⁺+1)

Example 171 (Compound 181)

[0237] In a manner similar to that in Example 15, Compound 181 (87.3 mg, 71%) was obtained from Compound 180 (100 mg, 0.270 mmol) prepared in Example 170, pyridine (65.4 μL, 0.810 mmol) and pivaloyl chloride (83.4 μL, 0.676 mmol).

AP-MS (m/z): 455 (M⁺+1)

Example 172 (Compound 182)

[0238] Compound 180 (60.6 mg, 0.170 mmol) obtained in Example 170 was dissolved in dichloromethane. To the solution was added pyridine (63.2 μL, 0.788 mmol) and 5-bromovaleryl chloride (23.0 μL, 0.172 mmol), and the mixture was stirred at room temperature for 5 hours. To the reaction mixture was added 1 mol/L hydrochloric acid and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was dissolved in dimethyl sulfoxide (0.3 mL). To the solution was added sodium acetate (58.7 mg), and the mixture was stirred at 100°C for 5 minutes. To the reaction mixture was added water (20 mL) and 1 mol/L hydrochloric acid (20 mL), and the mixture was extracted with chloroform. And then, the organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography (chloroform/acetone/ethyl acetate/n-hexane = 9/1/1/1) to obtain Compound 182 (42.5 mg, 45%).

AP-MS (m/z): 453 (M⁺+1)

Example 173 (Compound 183)

[0239] Compound 180 (100 mg, 0.270 mmol) prepared in Example 170 and pyridine (31.5 μL, 0.389 mmol) were dissolved in dichloromethane (2 mL). To the solution was added 4-bromobutyryl chloride (37.5 μL, 0.324 mmol) at 0°C, and the mixture was stirred at room temperature for 5 hours. To the reaction mixture was added 1 mol/L hydrochloric acid, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. To the residue was added methanol (20 mL) and potassium carbonate (1.0 g), and the mixture was vigorously stirred at room temperature for 20 minutes. To the reaction mixture was added water and 1 mol/L hydrochloric acid, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was purified by silica gel column chromatography (chloroform/acetone/ethyl acetate/n-hexane = 9/1/1/1) to obtain Compound 183 (27.6 mg, 37%).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.15 (d, J = 6.6 Hz, 6H), 2.22 (m, 2H), 2.55-2.67 (m, 3H), 2.94 (s, 3H), 3.31-3.47 (m, 3H), 3.61 (m, 1H), 3.91-3.98 (m, 2H), 5.0 (br s, 1H), 7.20-7.35 (m, 5H)

AP-MS (m/z): 437 (M⁺-1)

Example 174 (Compound 184)

[0240] In a manner similar to that in Example 173, Compound 180 (84.1 mg, 0.227 mmol) prepared in Example 170 was treated with pyridine (88.0 μL, 1.09 mmol) and 5-bromovaleryl chloride (121 μL, 0.908 mmol), and then treated with methanol and potassium carbonate (1.0 g) to obtain Compound 184 (89.1 mg, 81%).

AP-MS (m/z): 485 (M⁺+1)

Example 175 (Compound 185)

[0241] In a manner similar to that in Step 3 of Example 92, Compound 185 (16.7 g, 85%) was obtained from 3-(methylsulfonylamino)propiofenone=thiosemicarbazone (14.4 g, 47.9 mmol), proplonyl chloride (16.7 mL, 192 mmol) and pyridine (18.6 mL, 230 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.12 (t, J = 7.5 Hz, 3H), 1.19 (t, J = 7.3 Hz, 3H), 2.37 (m, 2H), 2.63 (m, 3H), 2.96 (s, 3H), 3.35 (m, 2H), 3.58 (m, 1H), 4.55 (br s, 1H), 7.20-7.35 (m, 5H), 8.01 (br s, 1H)

Example 176 (Compound 186)

[0242] In a manner similar to that in Example 170, Compound 186 (11.7 g, 81%) was obtained from Compound 185 (16.7 g, 40.5 mmol) prepared in Example 175, cerium chloride heptahydrate (15.1 g, 40.5 mol) and sodium borohydride (12.8 g, 338 mol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.13 (t, J = 8.7 Hz, 3H), 2.61-2.71 (m, 3H), 2.97 (s, 3H), 3.27-3.47 (m, 2H), 3.60-3.67 (m, 1H), 4.21 (br s, 2H), 4.65 (br s, 1H), 7.26-7.36 (m, 5H)

Example 177 (Compound 187)

[0243] In a manner similar to that in Example 15, Compound 187 (90.3 mg, 76%) was obtained from Compound 186 (96.0 mg, 0.269 mmol) prepared in Example 176, pyridine (65.4 μL, 0.810 mmol) and pivaloyl chloride (83.4 μL, 0.676 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.13 (t, J = 6.0 Hz, 3H), 1.28 (s, 9H), 2.66 (m, 3H), 2.97 (s, 3H), 3.35 (m, 2H), 3.61 (m, 1H), 4.58 (br s, 1H), 7.32 (m, 5H), 8.08 (br s, 1H) AP-MS (m/z): 441 (M⁺+1)

Example 178 (Compound 188)

[0244] In a manner similar to that in Example 172, Compound 188 (42.5 mg, 45%) was obtained from Compound 186 (100 mg, 0.221 mmol) prepared in Example 176, pyridine (85 μL, 1.05 mmol), 4-bromobutyryl chloride (110 μL, 0.949 mmol) and potassium carbonate (1.0 g).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.14 (t, J = 7.5 Hz, 3H), 2.19 (m, 2H), 2.50-2.81 (m, 5H), 2.96 (s, 3H), 3.35 (m, 2H), 3.59 (m, 1H), 3.93 (m, 2H), 4.52 (br s, 1H), 7.20-7.34 (m, 5H)

AP-MS (m/z): 424 (M-1)

Example 179 (Compound 189)

[0245] In a manner similar to that in Example 172, Compound 189 (27.6 mg, 37%) was obtained from Compound 186 (60.6 mg, 0.170 mmol) prepared in Example 176, pyridine (63.2 μL, 0.788 mmol), 5-bromovaleryl chloride (110 μL, 0.949 mmol) and potassium carbonate (1.0 g).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.14 (t, J = 7.5 Hz, 3H), 1.79-1.99 (m, 4H), 2.54-2.75 (m, 5H), 2.96 (s, 3H), 3.19-3.27 (m, 2H), 3.57-3.68 (m, 1H), 3.83-3.95 (m, 2H), 4.36 (br s, 1H), 7.20-7.37 (m, 5H)

AP-MS (m/z): 439 (M⁺+1)

Example 180 (Compound 190)

[0246] In a manner similar to that in of Example 170, Compound 190 (86.5 mg, 0.248 mmol) was obtained from Compound 105 (1.01 g, 2.33 mmol) prepared in Example 98 and sodium borohydride (2.20 g, 58.2 mmol):

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.30 (s, 9H), 2.37-2.46 (m, 1H), 2.63-2.86 (m, 2H), 3.41-3.51 (m, 1H), 3.71 (s, 3H), 4.09 (br s, 2H), 7.22-7.43 (m, 5H) Example 181 (Compound 191)

[0247] Compound 191 (89.5 mg, 29%) was obtained in the same manner as that in Example 133 from Compound 190 (86.5 mg, 0.248 mmol) obtained in Example 180 and 4-bromobutyryl chloride (57 μL, 0.495 mmol).

AP-MS (m/z): 496 (M-1)

Example 182 (Compound 192)

[0248] Compound 191 (89.5mg, 0.18mmol) prepared in Example 181 was dissolved in N,N-dimethylformamide (2.0 mL). To the solution was added 60% sodium hydride (14 mg, 0.359 mmol), and the mixture was stirred at room temperature for 1 hour. To the reaction mixture was added acetic acid and water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated saline, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 2/1) to obtain Compound 192 (30.2 mg, 40%).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.36 (s, 9H), 2.17-2.42 (m, 3H), 2.53-2.84 (m, 4H), 3.38-3.50 (s, 1H), 3.72 (s, 3H), 3.97 (m, 2H), 7.22-7.39 (m, 5H)

Example 183 (Compound 193)

[0249] In a manner similar to that in Example 99, Compound 193 (21.7mg, 74%) was obtained from Compound 192

(30.2 mg, 0.723 mmol) prepared in Example 182 and sodium hydroxide (8.7 mg, 0.217 mmol).
AP-MS (m/z): 402 (M-1)

Example 184 (Compound 194)

[0250] In a manner similar to that in Example 100, Compound 194 (7.3 mg, 30%) was obtained from Compound 193 (21.7 mg, 0.054 mmol) prepared in Example 183, oxalyl chloride (0.25 ml) and 2-aminoethanol (16 μ L, 26.9 mmol).
¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.34 (s, 9H), 2.17-2.28 (m, 3H), 2.54-2.82 (m, 2H), 3.34-3.46 (m, 3H), 3.72 (dd, J = 4.0, 6.0 Hz, 2H), 3.96 (br q, J = 7.0 Hz, 2H), 7.32-7.34 (m, 5H)

Example 185 (Compound 195)

[0251]

Step 1: In a manner similar to that in Step 1 of Example 1, 2-acetoxy-1-indanone=thiosemicarbazone (3.23 g, 57%) was obtained from 2-acetoxy-1-indanone (4.1 g, 21.6 mmol) and thiosemicarbazide hydrochloride (3.0 g, 23.7 mmol).

Step 2: In a manner similar to that in Step 2 of Example 1, 3-acetyl-5-aminospiro[1,3,4-thiadiazolin-2,1'-indan]-2'-yl acetate (187.4 mg, 48%) was obtained from 2-acetoxy-1-indanone=thiosemicarbazone (335.5 mg, 1.27 mmol) prepared above, pyridine (13 mL) and acetic anhydride (136 μ L, 1.53 mmol).

Step 3: 3-Acetyl-5-aminospiro[1,3,4-thiadiazolin-2,1'-indan]-2'-yl acetate (163.8 mg) prepared above was dissolved in dichloromethane (2.0 mL). To the solution was added pyridine (520 μ L, 6.44 mmol) and pivaloyl chloride (661 μ L, 5.36 mmol), and the mixture was stirred at room temperature for 24 hours. To the reaction mixture was added water and chloroform, and the mixture was extracted with chloroform. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/ethyl acetate = 3/2) to obtain Compound 195 (118.0 mg, 57%) as a diastereoisomer mixture. AP-MS (m/z): 390 (M⁺+1)

Example 186 (Compound 196)

[0252] Compound 195 (90.3 mg, 0.233 mmol) prepared in Example 185 was dissolved in methanol solution of 10% ammonia (4.8 mL), and the solution was allowed to stand at room temperature for 6 hours. The reaction mixture was concentrated, and then the residue was purified by silica gel column chromatography (chloroform/ethyl acetate = 3/2) to obtain Compound 196 (16.6 mg, 20%) as a diastereoisomer mixture.

FAB-MS (m/z): 348 (M⁺+1)

Example 187 (Compound 197)

[0253]

Step 1: In a manner similar to that in Step 1 of Example 1, 4-acetoxy-1-indanone=thiosemicarbazone (2.78 g, 80%) was obtained from 4-acetoxy-1-indanone (2.51 g, 13.2 mmol) and thiosemicarbazide hydrochloride (1.85 g, 14.5 mmol).

Step 2: In a manner similar to that in Example 11, Compound 197 (193.9 mg, 39%) was obtained from 4-acetoxy-1-indanone=thiosemicarbazone (364.5 mg, 1.38 mmol) prepared above, acetic anhydride (123 μ L, 1.38 mmol) and pyridine (112 μ L, 1.38 mmol).

¹H NMR (300 MHz, CDCl₃) δ (ppm): 2.18 (s, 3H), 2.30 (s, 3H), 2.59-2.68 (m, 1H), 2.76-2.86 (m, 1H), 3.09-3.30 (m, 2H), 4.17 (br s, 2H), 6.99 (dd, J = 7.7, 1.5 Hz, 1H), 7.31 (m, 2H)

Example 188 (Compound 198)

[0254] In a manner similar to that in Example 15, Compound 198 (136 mg, 98%) was obtained from Compound 197 (108.8 mg, 0.356 mmol) prepared in Example 187, pyridine (346 μ L, 4.28 mmol) and pivaloyl chloride (439 μ L, 3.56 mmol).

¹H NMR (270 MHz, CDCl₃) δ (ppm): 1.34 (s, 9H), 2.18 (s, 3H), 2.29 (s, 3H), 2.56-2.63 (m, 1H), 2.79-2.92 (m, 1H), 3.08-3.22 (m, 2H), 6.98-7.03 (m, 1H), 7.28-7.31 (m, 2H), 8.08 (br s, 1H)

Example 189 (Compound 199).

[0255] In a manner similar to that in Example 186, Compound 199 (70.0 mg, 94%) was obtained from Compound 198 (83.1 mg, 0.214 mmol) prepared in Example 188 and methanol solution of 10% ammonia (4.2 mL).

¹H NMR (300 MHz, CDCl₃) δ (ppm): 1.34 (s, 9H), 2.21 (s, 3H), 2.58-2.67 (m, 1H), 2.81-2.91 (m, 1H), 3.07-3.27 (m, 2H), 5.25 (br s, 1H), 6.62 (d, J= 7.7 Hz, 1H), 6.94 (d, J= 7.7 Hz, 1H), 7.10 (t, J= 7.7 Hz, 1H), 7.99 (br s, 1H)

Example 190 (Tablets)

[0256] Tablets comprising the following composition are obtained according to the conventional method.

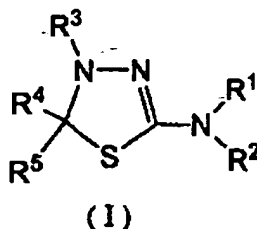
Compound 1	5 mg
Lactose	60 mg
Potato starch	30 mg
Polyvinyl alcohol	2 mg
Magnesium stearate	1 mg
Tar dye	trace

Industrial Applicability

[0257] The present invention provides a thiadiazoline derivative or a pharmacologically acceptable salt thereof which is useful for therapeutic treatment of a human malignant tumor, for example, breast cancer, gastric cancer, ovarian cancer, colon cancer, lung cancer, brain tumor, laryngeal cancer, hematological cancer, urinary or genital tumor including bladder cancer and prostatic cancer, renal cancer, skin carcinoma, hepatic carcinoma, pancreatic cancer, or uterine cancer, or the like. In addition, the present invention provides an antitumor agent comprising a thiadiazoline derivative or a pharmacologically acceptable salt thereof as an active ingredient.

Claims

1. An antitumor agent which comprises a thiadiazoline derivative represented by the general formula (I) or a pharmacologically acceptable salt thereof as an active ingredient:



< wherein R¹ and R⁴ are the same or different and each represents

a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocyclic group, or substituted or unsubstituted aryl;

R² represents

a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted cycloalkyl,

-C(=W)R⁶ [wherein

W represents

an oxygen atom or a sulfur atom

R⁶ represents

a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, a substituted or unsubstituted heterocyclic group,

-NR⁷R⁸ (wherein

R⁷ and R⁸ are the same or different and each represents

a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or a substituted or unsubstituted heterocyclic group, or

R⁷ and R⁸ are combined together with the adjacent nitrogen atom to form a substituted or unsubstituted heterocyclic group),

-OR⁹ (wherein

R⁹ represents

substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted aryl), or

-SR¹⁰ (wherein

R¹⁰ represents

substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted aryl)]

-NR¹¹R¹² (wherein

R¹¹ and R¹² are the same or different and each represents

a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted cycloalkyl, or

-C(=O)R¹³ (wherein

R¹³ represents

substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted aryl, a substituted or unsubstituted heterocyclic group,

-NR^{7A}R^{8A} (wherein R^{7A} and R^{8A} have the same meanings as those of the aforementioned R⁷ and R⁸, respectively), or

-OR^{9A} (wherein R^{9A} has the same meaning as that of the aforementioned R⁹)), or

-SO₂R¹⁴ (wherein

R¹⁴ represents

substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted aryl, or a substituted or unsubstituted heterocyclic group), or

R¹ and R² are combined together with the adjacent nitrogen atom to form a substituted or unsubstituted heterocyclic group,

R⁵ represents

substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocyclic group or substituted or unsubstituted aryl, or

R⁴ and R⁵ are combined to represent

-(CR²⁸R²⁹)_{m1}-Q-(CR^{28A}R^{29A})_{m2} (wherein

Q represents

a single bond, substituted or unsubstituted phenylene, or cycloalkylene,

m₁ and m₂ are the same or different and each represents

an integer of from 0 to 4, with the proviso that m₁ and m₂ are not 0 at the same time,

R²⁸, R²⁹, R^{28A} and R^{29A} are the same or different and each represents

a hydrogen atom, substituted or unsubstituted lower alkyl,

-OR³⁰ (wherein

R³⁰ represents

a hydrogen atom,

substituted or unsubstituted lower alkyl,

substituted or unsubstituted lower alkenyl,

-CONR³¹R³² (wherein

R³¹ and R³² are the same or different.

and each represents

a hydrogen atom, substituted or unsubstituted lower alkyl, a substituted or unsubstituted

heterocyclic group, or substituted or unsubstituted aryl),

-SO₂NR³³R³⁴ (wherein
R³³ and R³⁴ are the same or different
and each represents

a hydrogen atom, substituted or unsubstituted lower alkyl, a substituted or unsubstituted heterocyclic group, or substituted or unsubstituted aryl), or

-COR³⁵ (wherein
R³⁵ represents

a hydrogen atom, substituted or unsubstituted lower alkyl, a substituted or unsubstituted heterocyclic group, or substituted or unsubstituted aryl)],

-NR³⁶R³⁷ (wherein
R³⁶ and R³⁷ are the same or different and each represents
a hydrogen atom,
substituted or unsubstituted lower alkyl,

-COR³⁸ (wherein
R³⁸ represents

a hydrogen atom, substituted or unsubstituted lower alkyl, a substituted or unsubstituted heterocyclic group, substituted or unsubstituted aryl, substituted or unsubstituted lower alkoxy, substituted or unsubstituted aryloxy, amino, substituted or unsubstituted lower alkylamino, substituted or unsubstituted di(lower alkyl)amino, or substituted or unsubstituted arylamino), or

-SO₂R³⁹ (wherein
R³⁹ represents

substituted or unsubstituted lower alkyl, a substituted or unsubstituted heterocyclic group, or substituted or unsubstituted aryl)], or

-CO₂R⁴⁰ (wherein
R⁴⁰ represents

a hydrogen atom, substituted or unsubstituted lower alkyl, or substituted or unsubstituted aryl),

and

when m₁ or m₂ is an integer of 2 or more, each R²⁸, R²⁹, R^{28A} and R^{29A} may be the same or different, respectively, and any two of R²⁸, R²⁹, R^{28A} and R^{29A} which are bound to the adjacent two carbon atoms may be combined to form a bond), and

R³ represents

a hydrogen atom or

-C(=W^A)R^{6A} (wherein W^A and R^{6A} have the same meanings as those of the aforementioned W and R⁶, respectively)>.

2. The antitumor agent according to claim 1, wherein R⁴ is substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocyclic group, or substituted or unsubstituted aryl, and R⁵ is substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocyclic group, or substituted or unsubstituted aryl, or R⁴ and R⁵ are combined to represent -(CR²⁸R²⁹)_{m1}-Q-(CR^{28A}R^{29A})_{m2}.

3. The antitumor agent according to claim 1, wherein R⁵ is substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted cycloalkyl.

4. The antitumor agent according to claim 1 or 2, wherein R⁵ is substituted or unsubstituted aryl, or a substituted or unsubstituted heterocyclic group.

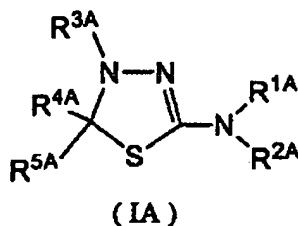
5. The antitumor agent according to claim 1 or 2, wherein R⁵ is substituted or unsubstituted phenyl, or substituted or unsubstituted thienyl.

6. The antitumor agent according to any one of claims 1 to 5, wherein R⁴ is substituted or unsubstituted lower alkyl.

7. The antitumor agent according to claim 1, wherein R⁴ and R⁵ are combined to represent -(CR²⁸R²⁹)_{m1}-Q-(CR^{28A}R^{29A})_{m2}.

8. The antitumor agent according to claim 1, wherein R⁴ and R⁵ are combined to represent -(CH₂)_{m1}-Q-(CH₂)_{m2}.

9. The antitumor agent according to claim 7 or 8, wherein Q is substituted or unsubstituted phenylene.
10. The antitumor agent according to any one of claims 1 to 9, wherein R¹ is a hydrogen atom, or substituted or unsubstituted lower alkyl.
11. The antitumor agent according to any one of claims 1 to 9, wherein R¹ is a hydrogen atom.
12. The antitumor agent according to any one of claims 1 to 11, wherein R² is -C(=W)R⁸.
13. The antitumor agent according to claim 12, wherein R⁸ is substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted cycloalkyl.
14. The antitumor agent according to claim 12 or 13, wherein W is an oxygen atom.
15. The antitumor agent according to any one of claims 1 to 9, wherein R¹ and R² are combined to form a substituted or unsubstituted heterocyclic group together with the adjacent nitrogen atom.
16. The antitumor agent according to any one of claims 1 to 15, wherein R³ is -C(=W^A)R^{6A}.
17. The antitumor agent according to claim 16, wherein R^{6A} is substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted cycloalkyl.
18. The antitumor agent according to claim 16, wherein R^{6A} is lower alkyl.
19. The antitumor agent according to any one of claims 16 to 18, wherein W^A is an oxygen atom.
20. A thiadiazoline derivative represented by the general formula (IA) or a pharmacologically acceptable salt thereof:



(wherein R^{1A}, R^{2A}, R^{3A}, R^{4A} and R^{5A} have the same meanings as those of the aforementioned R¹, R², R³, R⁴ and R⁵, respectively, with the proviso that when R^{2A} and R^{3A} are the same to be -CONHR^{8B} (wherein R^{8B} represents substituted or unsubstituted lower alkyl, or substituted or unsubstituted aryl), and

- (i) R^{4A} is a hydrogen atom, or
- (ii) one of R^{4A} and R^{5A} is substituted or unsubstituted lower alkyl,

then the other of R^{4A} and R^{5A} only represents substituted or unsubstituted cycloalkyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted lower alkynyl
[provided that

- (a) when R^{1A}, R^{2A} and R^{3A} are hydrogen atoms, and one of R^{4A} and R^{5A} is methyl, the other of R^{4A} and R^{5A} is not any of phenyl, 4-nitrophenyl, 4-aminophenyl, 4-bromophenyl, 3-nitrophenyl and 4-methoxy-3-nitrophenyl,
- (b) when R^{1A} and R^{2A} are hydrogen atoms, R^{3A} is acetyl,
 - (i) and one of R^{4A} and R^{5A} is methyl, the other of R^{4A} and R^{5A} is not any of methyl, ethyl, phenyl, 4-methoxyphenyl, 2-naphthylsulfonylmethyl, 4-bromophenylsulfonylmethyl and 4-chlorophenylsulfonylmethyl, and

(ii) and R^{4A} is a hydrogen atom,

R^{5A} is not any of phenyl, 4-nitrophenyl, 4-chlorophenyl, 4-methoxyphenyl, 4-dimethylaminophenyl and pyridyl,

(c) when R^{1A} is a hydrogen atom, R^{2A} and R^{3A} are acetyl,

(i) and one of R^{4A} and R^{5A} is methyl,

the other of R^{4A} and R^{5A} is not any of methyl, ethyl, propyl, butyl, hexyl, heptyl, phenyl, benzyl, acetyl-methyl, tert-butoxycarbonylmethyl, ethoxycarbonylmethyl, 4-bromophenylsulfonylmethyl, 4-bromophenylsulfonylethyl, 4-chlorophenylsulfonylmethyl, 3,4-dichlorophenylsulfonylmethyl, 3,4-dichlorophenylsulfonylethyl, 3,4-dimethylphenylsulfonylmethyl, phenylsulfonylmethyl, 4-methylphenylsulfonylmethyl, 4-methylphenylsulfonylethyl, 4-(acetylamino)phenylsulfonylethyl, 2-(4-bromophenylsulfonyl)-2-phenylethyl, 2-(4-methylphenylthio)-2-phenylethyl, 2-naphthylsulfonylethyl, 2-naphthylsulfonylmethyl, phenethyl, 3-benzoyloxyphenyl, 2-oxo-2H-1-benzopyran-3-yl, 2-furyl, 5-nitro-2-furyl, 5-methyl-2-furyl, 2-thienyl, 5-chloro-2-thienyl, 3-acetoxyphenyl, 3-nitrophenyl, 4-nitrophenyl, 4-fluorophenyl, 3-acetylaminophenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-ethylphenyl, 4-methylphenyl, 4-bromophenyl, 4-nonyloxyphenyl, 4-phenylphenyl, 3,4-dimethoxyphenyl, 1,3-benzodioxol-5-yl, 4-(benzimidazol-2-ylamino)phenyl, 4-(1-methylbenzimidazol-2-ylamino)phenyl, 3-pyridyl, 2-naphthyl, 2-acetylamino-4-acetyl-1,3,4-thiadiazolin-5-yl and 4-acetylaminophenylsulfonylmethyl,

(ii) and one of R^{4A} and R^{5A} is phenyl,

the other of R^{4A} and R^{5A} is not any of phenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 4-nitrophenyl, ethoxycarbonylmethyl, isobutyl, sec-butyl, n-butyl and acetylaminomethyl,

(iii) and one of R^{4A} and R^{5A} is 2-acetoxyphenyl,

the other of R^{4A} and R^{5A} is not 2-phenylethenyl,

(iv) and R^{4A} is a hydrogen atom or 4-methoxyphenyl,

R^{5A} is not 4-methoxyphenyl,

(v) and R^{4A} is a hydrogen atom,

R^{5A} is not any of phenyl, 4-nitrophenyl, 4-chlorophenyl, 4-dimethylaminophenyl and pyridyl,

(vi) and R^{4A} and R^{5A} are combined to represent

-(CH₂)_{m1}-Q-(CH₂)_{m2}- (wherein m₁, m₂ and Q have the same meanings as those of the aforementioned, respectively),

-(CH₂)_{m1}-Q-(CH₂)_{m2}- wherein Q is single bond and the sum of m₁ and m₂ is 5, is excluded

(vii) and one of R^{4A} and R^{5A} is 1,2,3-triacetoxypropyl,

the other of R^{4A} and R^{5A} is not 3,4-dihydro-3-oxo-2-quinoxaliny, and

(viii) and one of R^{4A} and R^{5A} is ethyl,

the other of R^{4A} and R^{5A} is not ethyl,

(d) when R^{1A} and R^{4A} are hydrogen atoms, and

(i) R^{2A} and R^{3A} are the same to be propionyl or benzoyl, or

(ii) R^{2A} is propionyl and R^{3A} is acetyl,

R^{5A} is not phenyl,

(e) when R^{1A} and R^{3A} are hydrogen atoms,

R^{2A} is acetyl, and

one of R^{4A} and R^{5A} is methyl,

the other of R^{4A} and R^{5A} is not either of phenyl and 3,4-dichlorophenylsulfonylethyl,

(f) when R^{1A} is phenyl, R^{2A} and R^{3A} are acetyl,

(i) and one of R^{4A} and R^{5A} is methyl,

the other of R^{4A} and R^{5A} is not either of 4-acetoxy-6-methyl-2-oxo-2H-pyran-3-yl and 2-oxo-2H-1-benzopyran-3-yl, and

(ii) and R^{4A} is phenyl,

R^{5A} is not phenyl,

(g) when R^{1A} is methyl, R^{2A} and R^{3A} are acetyl,

(i) and R^{4A} is a hydrogen atom,

R^{5A} is not phenyl,
 (ii) and one of R^{4A} and R^{5A} is methyl,
 the other of R^{4A} and R^{5A} is not either of ethoxycarbonylethyl and ethoxycarbonylpropyl,

- 5 (h) when R^{1A}, R^{2A} and R^{4A} are methyl, and
 R^{5A} is pyridyl,
 R^{3A} is not -CORC (wherein R^C represents methyl, chloromethyl, methoxy, ethoxycarbonylmethyl or
 ethoxycarbonylethenyl),
 (i) when one of R^{1A} and R^{2A} is a hydrogen atom,
 10 the other of R^{1A} and R^{2A} is ethyl, and
 R^{3A} is a hydrogen atom or acetyl,
 R^{4A} and R^{5A} are not methyl at the same time,
 (k) when R^{1A} is 4-chlorophenyl,
 R^{2A} is a hydrogen atom, and
 15 one of R^{4A} and R^{5A} is methyl,
 the other of R^{4A} and R^{5A} is not (1-methylbenzimidazol-2-ylamino)phenyl, and R^{3A} is not acetyl,
 (m) when R^{1A} is phenyl, 4-chlorophenyl, 4-methylphenyl or
 4-methoxyphenyl,
 R^{2A} is a hydrogen atom, and
 20 R^{4A} and R^{5A} are methyl,
 R^{3A} is not any of acetyl, 4-chlorophenoxyacetyl, 2-chlorophenoxyacetyl, 3-methylphenoxyacetyl and
 phenylaminocarbonyl,
 (n) when R^{2A} and R^{3A} are acetyl,
 one of R^{4A} and R^{5A} is methyl,
 25 (i) and the other of R^{4A} and R^{5A} is 1H-benzotriazol-1-ylmethyl,
 R^{1A} is not any of cyclohexyl, benzyl, phenyl, 2-methylphenyl and 4-methoxyphenyl,
 (ii) and the other of R^{4A} and R^{5A} is 2-methylbenzimidazol-1-ylmethyl or 2-ethylbenzimidazol-1-ylmethyl,
 R^{1A} is not any of cyclohexyl, phenyl and 4-bromophenyl,
 30 (o) when R^{1A} is a hydrogen atom,
 R^{2A} is acetyl, and
 R^{4A} and R^{5A} are methyl,
 R^{3A} is not benzoyl,
 (p) when one of R^{1A} and R^{2A} is a hydrogen atom,
 35 the other of R^{1A} and R^{2A} is methyl, and
 R^{4A} and R^{5A} are both methyl or both ethyl,
 R^{3A} is not any of acetyl, benzoyl, pivaloyl, 3-nitrobenzoyl, 2-fluorobenzoyl, 4-fluorobenzoyl, 2-trifluoromethylbenzoyl and 3-trifluoromethylbenzoyl, and
 (q) when R^{1A} is methyl,
 40 R^{2A} is methylaminocarbonyl, and
 R^{4A} and R^{5A} are both methyl or both ethyl,
 R^{3A} is not any of acetyl, benzoyl, pivaloyl, 2-fluorobenzoyl, 4-fluorobenzoyl, 2-trifluoromethylbenzoyl,
 3-trifluoromethylbenzoyl and 4-trifluoromethylbenzoyl].

45 21. The thiadiazoline derivative according to claim 20, wherein R^{4A} is substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, or substituted or unsubstituted lower alkenyl, R^{5A} is substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocyclic group, or substituted or unsubstituted aryl, or R^{4A} and R^{5A} are combined to represent $-(CR^{28}R^{29})_{m1}-Q-(CR^{28A}R^{29A})_{m2}-$ (wherein R²⁸, R²⁹, R^{28A}, R^{29A}, m₁, m₂ and Q have the same meanings as those of the aforementioned, respectively), or the pharmacologically acceptable salt thereof.
 50

22. The antitumor agent according to claim 20, wherein R^{5A} is substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted cycloalkyl.

55 23. The thiadiazoline derivative according to claim 20 or 21, wherein R^{5A} is substituted or unsubstituted aryl, or a substituted or unsubstituted heterocyclic group, or the pharmacologically acceptable salt thereof.

24. The thiadiazoline derivative according to claim 20 or 21, wherein R^{5A} is substituted or unsubstituted phenyl, or

- substituted or unsubstituted thienyl, or the pharmacologically acceptable salt thereof.
25. The thiadiazoline derivative according to any one of claims 20 to 24, wherein R^{4A} is substituted or unsubstituted lower alkyl, or the pharmacologically acceptable salt thereof.
 26. The thiadiazoline derivative according to any one of claims 20 to 24, wherein R^{4A} is substituted lower alkyl, or the pharmacologically acceptable salt thereof.
 27. The thiadiazoline derivative according to claim 20, wherein R^{4A} and R^{5A} are combined to represent $-(CR^{28}R^{29})_{m1}-Q-(CR^{28A}R^{29A})_{m2}-$ (wherein R^{28} , R^{29} , R^{28A} , R^{29A} , $m1$, $m2$ and Q have the same meanings as those of the aforementioned, respectively), or the pharmacologically acceptable salt thereof.
 28. The thiadiazoline derivative according to claim 20, wherein R^{4A} and R^{5A} are combined to represent $-(CH_2)_{m1}-Q-(CH_2)_{m2}-$ (wherein $m1$, $m2$ and Q have the same meanings as those of the aforementioned, respectively), or the pharmacologically acceptable salt thereof.
 29. The thiadiazoline derivative according to claim 27 or 28, wherein Q is substituted or unsubstituted phenylene, or the pharmacologically acceptable salt thereof.
 30. The thiadiazoline derivative according to any one of claims 20 to 29, wherein R^{1A} is a hydrogen atom or substituted or unsubstituted lower alkyl, or the pharmacologically acceptable salt thereof.
 31. The thiadiazoline derivative according to any one of claims 20 to 29, wherein R^{1A} is a hydrogen atom, or the pharmacologically acceptable salt thereof.
 32. The thiadiazoline derivative according to any one of claims 20 to 31, wherein R^{2A} is $-C(=W)R^6$ (wherein W and R^6 have the same meanings as those of the aforementioned, respectively), or the pharmacologically acceptable salt thereof.
 33. The thiadiazoline derivative according to claim 32, wherein R^6 is substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted cycloalkyl, or the pharmacologically acceptable salt thereof.
 34. The thiadiazoline derivative according to claim 32 or 33, wherein W is an oxygen atom, or the pharmacologically acceptable salt thereof.
 35. The thiadiazoline derivative according to any one of claims 20 to 29, wherein R^{1A} and R^{2A} are combined together with the adjacent nitrogen atom to form a substituted or unsubstituted heterocyclic group, or the pharmacologically acceptable salt thereof.
 36. The thiadiazoline derivative according to any one of claims 20 to 35, wherein R^{3A} is $-C(=W^A)R^{6A}$ (wherein W^A and R^{6A} have the same meanings as those of the aforementioned, respectively), or the pharmacologically acceptable salt thereof.
 37. The thiadiazoline derivative according to claim 36, wherein R^{6A} is substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted cycloalkyl, or the pharmacologically acceptable salt thereof.
 38. The thiadiazoline derivative according to claim 36, wherein R^{6A} is lower alkyl, or the pharmacologically acceptable salt thereof.
 39. The thiadiazoline derivative according to any one of claims 36 to 38, wherein W^A is an oxygen atom, or the pharmacologically acceptable salt thereof.
 40. A pharmaceutical composition which comprises the thiadiazoline derivative according to any one of claims 20 to 39 or a pharmacologically acceptable salt thereof as an active ingredient.
 41. An antitumor agent which comprises the thiadiazoline derivative according to any one of claims 20 to 39 or a

pharmacologically acceptable salt thereof as an active ingredient.

42. Use of the thiadiazoline derivative according to any one of claims 20 to 39 or a pharmacologically acceptable salt thereof for the manufacture of an antitumor agent.

43. A method for the treatment of a malignant tumor comprising administering an effective amount of the thiadiazoline derivative according to any one of claims 20 to 39 or a pharmacologically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP02/12961

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl.⁷ C07D285/135, 417/04, 285/14, A61K31/433, 31/4439, 31/497, 31/5377, A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl.⁷ C07D285/135, 417/04, 285/14, A61K31/433, 31/4439, 31/497, 31/5377, A61P35/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS (STN), CAOLD (STN), REGISTRY (STN), WPI/L (DIALOG)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4338449 A (ELI LILLY AND CO.), 06 July, 1982 (06.07.82), All pages (Family: none)	20, 22, 25-26, 30, 32-34, 36-39
X	M.A. Khalil, et al., Synthesis and antimicrobial evaluation of novel oxa(thia)diazolylquinolines and oxa(thia)diazepino[7,6-b]quinolines, Arch. Pharm. (Weinheim) 1993, Vol.326, pages 489 to 492; compounds 5a to 5d described on page 491	20, 23, 32-34, 36-40
X	Ahmed A. Farghaly, et al., Design and synthesis of some oxadiazolyl, thiadiazolyl, and thiazolyl derivatives of 1H-pyrazoles as anti-inflammatory antimicrobial agents, Arch.Pharm.Pharm.Med.Chem., 2000, Vol.333, No.2-3, pages 53 to 57; compounds 7a to 7c described on page 54	20, 23, 32-34, 36-40

☒ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not
considered to be of particular relevance"B" earlier document but published on or after the international filing
date"L" document which may throw doubts on priority claim(s) or which is
cited to establish the publication date of another citation or other
special reason (as specified)"O" document referring to an oral disclosure, use, exhibition or other
means"P" document published prior to the international filing date but later
than the priority date claimed"T" later document published after the international filing date or
priority date and not in conflict with the application but cited to
understand the principle or theory underlying the invention"X" document of particular relevance; the claimed invention cannot be
considered novel or cannot be considered to involve an inventive
step when the document is taken alone"Y" document of particular relevance; the claimed invention cannot be
considered to involve an inventive step when the document is
combined with one or more other such documents, such
combination being obvious to a person skilled in the art

"Z" document member of the same patent family

Date of the actual completion of the international search
05 February, 2003 (05.02.03)Date of mailing of the international search report
01 April, 2003 (01.04.03)Name and mailing address of the ISA/
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Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP02/12961

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	El-Sayada M. El-Khawass, et al., Synthesis of novel pyrazolylpyrazole, pyrazolylthiadiazole and pyrazolylthiazoline derivatives as potential anti-inflammatory agents, Alexandria Journal of Pharmaceutical Sciences, 1990, Vol.4, No.1, pages 77 to 79; compounds VIa to VIc described on page 79	20, 23, 30-34, 36-40
X	Hassan M. Mokhtar, et al., 3-(Ethoxycarbonyl)-2-methylpyrrole-5-carboxaldehyde as a versatile synthon for potential antibacterial agents, Bull. Pharm. Sci., Assiut University, 1995, Vol.18, No.2, pages 59 to 67; compounds VIIa, c, d, e described on page 64	20, 23, 30-34, 36-40
X	Chemical Abstracts, 1989, Vol.114, abstract No. 62034 & Khalil, Mounir A. et al., Synthesis of novel oxazolidine and thiadiazoline derivatives of 4(3H)-quinazolinone as potential anti-microbial agents, Alexandria Journal of Pharmaceutical Sciences, 1989, Vol.3, No.2, pages 221 to 224	20, 23, 30-34, 36-40
X	Chemical Abstracts, 1989, Vol.114, abstract No. 42661 & Awad, Laila L. et al., Synthesis of some 5-(2-phenyl-1,2,3-triazol-4-yl)-4,5-dihydro-1,3,4-thiadiazoles, Alexandria Journal of Pharmaceutical Sciences, 1989, Vol.3, No.2, pages 119 to 121	20, 23, 30-34, 36-39
X	Seham Y. Hassan, et al., Synthesis and reactions of 2-methyl-3-substituted pyrrole or (furan)-5-thiosemicarbazone derivatives, J.Saudi.Chem.Soc., 1999, Vol.3, No.2, pages 171 to 176; compounds 13 to 19 described on page 175	20, 23-24, 30
X	Tian-Bao Huang, et al., Reaction of schiff base of thiohydrazides with P(NR ₂) ₃ , Phosphorus, Sulfur and Silicon and the Related Elements, 1997, Vol.122, pages 307 to 312; compound 5 described on page 309	20, 30-34, 36-39
Y	Baerbel Schulze, et al., Acylation from thiocyanatovinylaldehyde thiosemicarbazones, Zeitschrift fuer Chemie, 1989, Vol.29, No.5, pages 166 to 167; compounds 3f, 3g described on page 167	1-11, 16-31, 36-42
Y	JP 2000-204077 A (Warner-Lambert Co.), 25 July, 2000 (25.07.00), Claims 1, 21, 26 to 29 (Family: none)	1-11, 16-31, 36-42
	JP 2000-229959 A (Sumitomo Pharmaceuticals Co., Ltd.),	

Form PCT/ISA/210 (continuation of second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP02/12961

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4927822 A (FISONS PLC), 22 March, 1990 (22.03.90), & EP 217519 A1 & JP 62-53976 A	1-42
A	WO 01/56994 A1 (BIOGEN INC.), 09 August, 2001 (09.08.01), & AU 3474101 A	1-42
A	WO 93/22311 A1 (E.I. Du Pont de Nemours & Co.), 11 November, 1993 (11.11.93), & AU 4288293 A	1-42

Form PCT/ISA/210 (continuation of second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP02/12961

Box I Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 43

because they relate to subject matter not required to be searched by this Authority, namely:

Claim 43 pertains to methods for treatment of the human body by therapy and thus relates to a subject matter which this International Searching Authority is not required, under the provisions of Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

2. ☐ Claims Nos.:

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

PATENT ABSTRACTS OF JAPAN

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(21)Application number : 07-118404

(71)Applicant : MITSUBISHI CHEM CORP

(22)Date of filing : 17.05.1995

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(30)Priority

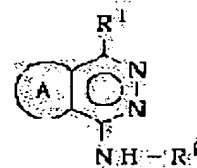
Priority number : 06105367 Priority date : 19.05.1994 Priority country : JP

(54) THERAPEUTIC OR PREVENTING AGENT FOR DISEASE CAUSED BY PROLIFERATION OF
SMOOTH MUSCULAR CELL

(57)Abstract:

PURPOSE: To obtain a therapeutic or preventing agent for diseases caused by the proliferation of smooth muscular cells containing a specific aminopyridazinone derivative as an active ingredient.

CONSTITUTION: This therapeutic or preventing agent for diseases caused by the proliferation of smooth muscular cells contains a compound of the formula [R1 is cyclohexyl or phenyl, thienyl or furyl which may respectively have a substituent group; R2 is CHR3R4 [R3 is H or a 1-4C alkyl; R4 is a 1-4C alkyl, cyclohexyl, thienyl or phenyl which may have a substituent group (a 1-4C alkyl, a 1-4C alkoxy or a halogen) or cyclohexyl which may have one or more substituent groups (a 1-4C alkyl, a 1-4C alkoxy and a 1-6C alkylene)]; ring A is benzene, thiophene or furan ring] or its salt, e.g. (R)-1-(1cyclohexylethylamino)-4-phenylphthalazine as an active ingredient. The medicine is useful for preventing or treating restenosis after the percutaneous transluminal coronary angioplasty (PTCA), angiostenosis after the organ transplantation and restenosis after the percutaneous transluminal angioplasty (PTA).



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C 0 7 D 237/34				
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(33) 優先権主張国 日本 (J P)

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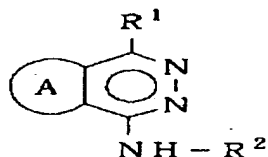
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(54) 【発明の名称】 平滑筋細胞増殖に起因する疾患の治療・予防剤

(57) 【要約】

【構成】 下記一般式 (I)

【化1】



R¹ : フェニル基、チエニル基、フリル基等

R² : -CHR³R⁴ 等 (R³ : アルキル基等、R⁴ : シクロヘキシル基等)

環A : ベンゼン環、チオフェン環等

で表されるアミノピリダジノン誘導体またはその塩を有効成分とする平滑筋細胞増殖に起因する疾患の治療・予防剤。

【効果】 アミノピリダジノン誘導体は、平滑筋細胞の遊走、増殖を抑制するので、平滑筋細胞増殖に起因する疾患、例えば経皮的冠動脈拡張術 (PTCA) 後の再狭窄、心臓、肝臓、腎臓、血管等の臓器移植後の血管狭

窄、経皮的動脈拡張術 (PTA) 後の再狭窄の予防もしくは治療に有用である。

【特許請求の範囲】

【請求項1】 下記一般式 (I)

【化1】



(I)

(上記式中で、 R^1 はシクロヘキシル基； $C_1 \sim C_4$ のアルキル基、 $C_1 \sim C_4$ のアルコキシ基およびハロゲン原子から選ばれる1以上の置換基を有していてもよいフェニル基； $C_1 \sim C_4$ のアルキル基、 $C_1 \sim C_4$ のアルコキシ基およびハロゲン原子から選ばれる1以上の置換基を有していてもよいチエニル基；または $C_1 \sim C_4$ のアルキル基、 $C_1 \sim C_4$ のアルコキシ基およびハロゲン原子から選ばれる1以上の置換基を有していてもよいフリル基を表し、 R^2 は $-\text{CHR}^3 \text{R}^4$ (R^3 は水素原子または $C_1 \sim C_4$ のアルキル基を表し、 R^4 は $C_1 \sim C_4$ のアルキル基；シクロヘキシル基；チエニル基；または $C_1 \sim C_4$ のアルキル基、 $C_1 \sim C_4$ のアルコキシ基およびハロゲン原子から選ばれる1以上の置換基を有していてもよいフェニル基を表す。) または $C_1 \sim C_4$ のアルキル基、 $C_1 \sim C_4$ のアルコキシ基および $C_1 \sim C_6$ のアルキレン基から選ばれる1以上の置換基を有していてもよいシクロヘキシル基を表し、環Aはベンゼン環、チオフェン環またはフラン環を表す。) で表されるアミノピリダジン誘導体またはその塩を有効成分とする平滑筋細胞増殖に起因する疾患の治療・予防剤。

【請求項2】 R^2 が $-\text{CHR}^3 \text{R}^4$ (R^3 は $C_1 \sim C_4$ のアルキル基を表し、 R^4 はシクロヘキシル基を表す。) を表すことを特徴とする請求項1記載の平滑筋細胞増殖に起因する疾患の治療・予防剤。

【請求項3】 R^1 がフェニル基、2-チエニル基または2-フリル基を表すことを特徴とする請求項1または2に記載の平滑筋細胞増殖に起因する疾患の治療・予防剤。

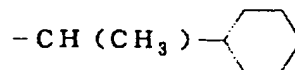
【請求項4】 R^1 がフェニル基を表すことを特徴とする請求項1または2に記載の平滑筋細胞増殖に起因する疾患の治療・予防剤。

【請求項5】 環Aがベンゼン環またはチオフェン環を表すことを特徴とする請求項1～4のいずれかに記載の平滑筋細胞増殖に起因する疾患の治療・予防剤。

【請求項6】 環Aがベンゼン環を表すことを特徴とする請求項1～4のいずれかに記載の平滑筋細胞増殖に起因する疾患の治療・予防剤。

【請求項7】 R^1 がフェニル基を表し、 R^2 が

【化2】



を表し、環Aがベンゼン環を表すことを特徴とする請求項1記載の平滑筋細胞増殖に起因する疾患の治療・予防剤。

【請求項8】 (R) - 1 - (1-シクロヘキシルエチルアミノ) - 4-フェニルフラジジンまたは薬学的に許容されるその塩を有効成分とする平滑筋細胞増殖に起因する疾患の治療・予防剤。

【請求項9】 平滑筋細胞増殖に起因する疾患が、経皮的冠動脈拡張術後の再狭窄である請求項1～8のいずれかに記載の治療・予防剤。

【請求項10】 平滑筋細胞増殖に起因する疾患が、臓器移植後の血管狭窄である請求項1～8のいずれかに記載の治療・予防剤。

【請求項11】 平滑筋細胞増殖に起因する疾患が、経皮的動脈拡張術後の再狭窄である請求項1～8のいずれかに記載の治療・予防剤。

【発明の詳細な説明】

【0001】

【産業上の利用分野】本発明は、平滑筋細胞増殖に起因する疾患の治療・予防剤に関し、詳細には特定のアミノピリダジン誘導体またはその塩を有効成分とする平滑筋細胞増殖に起因する疾患の治療・予防剤に関する。

【0002】

【従来の技術および発明が解決しようとする課題】近年、狭小化した血管を外科的に治療する方法として、経皮的冠動脈拡張術 (Percutaneous Transluminal Coronary Angioplasty: PTCA)、経皮的動脈拡張術 (Percutaneous Transluminal Angioplasty: PTA) が普及しつつある。これらは大腿動脈などからバルーンカテーテルを遠隔的に挿入してゆき、狭窄部でバルーンを膨らませ、物理的に血管を拡張させるものである。しかしこの治療法の場合、施行後3～6ヶ月で再び狭窄が起きることがある。この再狭窄では、コレステロールの沈着は観察されず、むしろそのほとんどを平滑筋細胞やこの細胞が産生する細胞間マトリックスによって構成された、いわゆる細胞線維性内膜肥厚である (Journal of American College of Cardiology vol. 23, (6), 1278-1288, 1994, May)。また、心臓、肝臓、腎臓、血管等の臓器移植後における血管狭窄も平滑筋細胞の増殖に起因している (FASEB Journal vol 7, 1055-1060, 1993, August)。

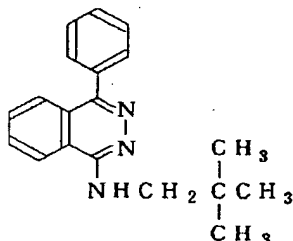
【0003】そのため、PTCA術およびPTA術後の再狭窄ならびに臓器移植後の血管狭窄の治療・予防法としては、血管内腔で生じる平滑筋細胞の遊走、増殖を抑

制することが有効であると考えられた。かかる課題を解決するべく、薬剤の探索が行われているが（特開昭 57-38715 号、特開平 2-121922 号、特開平 3-83923 号、特開平 3-83957 号、特開平 3-118383 号、特開平 4-99775 号、特開平 4-154720 号各公報等）、未だ開発に至っていないのが現状である。

【0004】一方、各種のフタラジン誘導体については各種の薬理作用が報告されている。例えば特開昭 56-53659 号公報、特開昭 56-53660 号公報および特開昭 57-48972 号公報には 1-アニリノ-4-フェニルフタラジン誘導体が、また特開昭 60-218377 号公報および特開昭 60-243074 号公報には下記の 2 化合物が *in vitro* で強力な血小板凝集抑制作用を有することが開示されている。

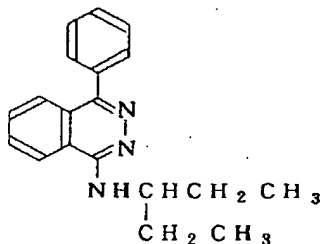
【0005】

【化 3】



【0006】

【化 4】



【0007】英国特許第 1303016 号、ジャーナル・オブ・メディシナル・ケミストリー (J. Med. Chem.)、12, 555 (1969) 等を開示されている 1-アミノ-4-フェニルフタラジン誘導体については、抗炎症作用や抗リチウム作用が記載されているのみである。

【0008】さらに、欧州公開特許公報第 449203 号（特開平 4-211666 号公報）には 1- α -置換ベンジルアミノ-4-フェニルフタラジン誘導体が、欧州公開特許公報第 534443 号には 3, 6-ジ置換ピリダジン誘導体が開示されている。両者はいずれも強力な血小板凝集抑制作用を有するものであり、同作用により、脳血栓、脳塞栓等の脳血管障害、心筋梗塞等の虚血性心疾患、末梢循環障害などの循環障害に対して効果が期待できることが開示されている。しかし、これらのフ

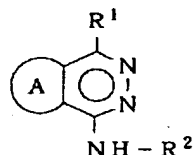
タラジン誘導体が平滑筋細胞増殖抑制作用を有することは知られていなかった。

【0009】

【課題を解決するための手段】本発明者らは、上記課題を解決する目的で検討を重ねてきた結果、血小板凝集抑制作用を有することが知られていたアミノピリダジン誘導体に血管内腔で生じる平滑筋細胞の増殖を抑制する作用があることを初めて見出し、本発明を完成するに至った。即ち本発明の要旨は、下記一般式 (I)

【0010】

【化 5】



(I)

【0011】{上記式中、 R^1 はシクロヘキシル基； $C_1 \sim C_4$ のアルキル基、 $C_1 \sim C_4$ のアルコキシ基およびハロゲン原子から選ばれる 1 以上の置換基を有していてもよいフェニル基； $C_1 \sim C_4$ のアルキル基、 $C_1 \sim C_4$ のアルコキシ基およびハロゲン原子から選ばれる 1 以上の置換基を有していてもよいチエニル基；または $C_1 \sim C_4$ のアルキル基、 $C_1 \sim C_4$ のアルコキシ基およびハロゲン原子から選ばれる 1 以上の置換基を有していてもよいフリル基を表し、 R^2 は $-CHR^3$ 、 R^4 (R^3 は水素原子または $C_1 \sim C_4$ のアルキル基を表し、 R^4 は $C_1 \sim C_4$ のアルキル基；シクロヘキシル基；チエニル基；または $C_1 \sim C_4$ のアルキル基、 $C_1 \sim C_4$ のアルコキシ基およびハロゲン原子から選ばれる 1 以上の置換基を有していてもよいフェニル基を表す。) または $C_1 \sim C_4$ のアルキル基、 $C_1 \sim C_4$ のアルコキシ基および $C_1 \sim C_6$ のアルキレン基から選ばれる 1 以上の置換基を有していてもよいシクロヘキシル基を表し、環 A はベンゼン環、チオフェン環またはフラン環を表す。} で表されるアミノピリダジン誘導体またはその塩を有効成分とする平滑筋細胞増殖に起因する疾患の治療・予防剤に存する。

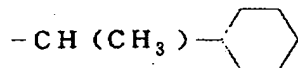
【0012】以下、本発明につき詳細に説明する。本発明の平滑筋細胞増殖に起因する疾患の治療・予防剤は、上記一般式 (I) のアミノピリダジン誘導体またはその塩を有効成分とする。上記一般式中の $C_1 \sim C_4$ のアルキル基としてはメチル基、エチル基、*n*-プロピル基、*i*-プロピル基、*n*-ブチル基、*t*-ブチル基等が挙げられ、 $C_1 \sim C_4$ のアルコキシ基としてはメトキシ基、エトキシ基、*n*-プロポキシ基、*i*-プロポキシ基、*n*-ブトキシ基、*t*-ブトキシ基等が挙げられ、ハロゲン原子としてはフッ素原子、塩素原子、臭素原子等が挙げられる。 $C_1 \sim C_6$ のアルキレン基としては、任意の 2 つの置換基が連結してメチレン基、エチレン基、トリメ

チレン基、テトラメチレン基、ペンタメチレン基、プロピレン基、エチルエチレン基、ジメチルメチレン基等を表すもの等が挙げられる。

【0013】 R^1 としてはフェニル基、2-チエニル基または2-フリル基が好ましく、特にフェニル基が好ましい。 R^2 としては $-\text{CHR}^3$ 、 R^4 （ R^3 は $\text{C}_1 \sim \text{C}_4$ のアルキル基を表し、 R^4 はシクロヘキシル基を表す。）が好ましく、特に

【0014】

【化6】



【0015】が好ましい。環Aとしてはベンゼン環またはチオフェン環を表す化合物が好ましく、特にベンゼン環が好ましい。

【0016】一般式(I)のアミノピリダジン誘導体が形成し得る塩としては、例えば塩酸塩、臭化水素酸塩、ヨウ化水素酸塩、硫酸塩、リン酸塩等の無機酸の塩、またはメタンスルホン酸塩、p-トルエンスルホン酸塩、

ベンゼンスルホン酸塩、カンファースルホン酸塩、酢酸塩、安息香酸塩、リンゴ酸塩、乳酸塩、グリコール酸塩、グルクロン酸塩、マレイン酸塩、フマル酸塩、シュウ酸塩、アスコルビン酸塩、クエン酸塩、サリチル酸塩、ニコチン酸塩、酒石酸塩等の有機酸の塩が挙げられる。一般式(I)の化合物およびその塩は水和物または溶媒和物の形で存在することもあるのでこれらの水和物、溶媒和物も本発明の化合物に含まれる。

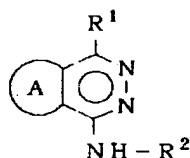
【0017】さらに上記一般式(I)のアミノピリダジン誘導体に不斉炭素が存在する場合は、(R)体、

(S)体、(RS)体のいずれをもとることができ、これらはすべて本発明の有効成分となる化合物に包含される。平滑筋細胞増殖に起因する疾患としては、具体的にはPTCA術後の再狭窄、心臓、肝臓、腎臓、血管等の臓器移植後の血管狭窄、PTA術後の再狭窄等が挙げられる。以下の表-1に本発明のアミノピリダジン誘導体の具体例を示す。

【0018】

【表1】

表-1



化合物 No.	R^1	R^2	A
1			
2			
3			
4			
5			
6			

【0019】

【表2】

表-1 (つづき)

7		$\begin{array}{c} \text{---CH---} \\ \\ \text{CH}_3 \end{array}$	
8		$\begin{array}{c} \text{---CH---} \\ \\ \text{C}_2\text{H}_5 \end{array}$	
9		$\begin{array}{c} \text{---CH---} \\ \\ \text{C}_4\text{H}_9 \end{array}$	
10		$\begin{array}{c} \text{---CH---} \\ \\ \text{CH}_3 \end{array}$	
11		$\begin{array}{c} \text{---CH---} \\ \\ \text{CH}_3 \end{array}$	
12		$\begin{array}{c} \text{---CH---} \\ \\ \text{CH}_3 \end{array}$	
13		$\begin{array}{c} \text{---CH---} \\ \\ \text{CH}_3 \end{array}$	
14		$\begin{array}{c} \text{---CH---} \\ \\ \text{CH}_3 \end{array}$	

【0020】

【表3】

表 - 1 (つづき)

15			
16			
17			
18			
19			
20			
21			
22			

【0021】

【表4】

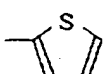

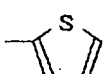

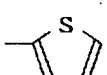

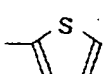

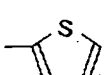

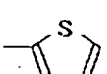

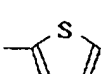

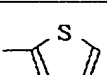

表-1 (つづき)

23		$\begin{array}{c} -\text{CH}-\text{H} \\ \\ \text{CH}_3 \end{array}$	
24		H	
25			
26		$\begin{array}{c} -\text{CH}-\text{C}_6\text{H}_5 \\ \\ \text{CH}_3 \end{array}$	
27		$\begin{array}{c} -\text{CH}-\text{H} \\ \\ \text{CH}_3 \end{array}$	
28		$\begin{array}{c} -\text{CH}-\text{C}_6\text{H}_5 \\ \\ \text{CH}_3 \end{array}$	
29		$\begin{array}{c} -\text{CH}-\text{H} \\ \\ \text{CH}_3 \end{array}$	
30		$\begin{array}{c} -\text{CH}-\text{C}_6\text{H}_5 \\ \\ \text{CH}_3 \end{array}$	

【0022】

【表5】

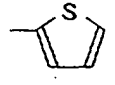

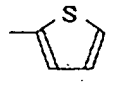

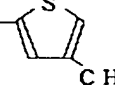

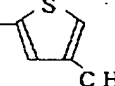

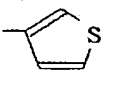

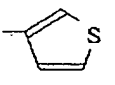

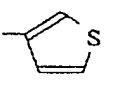

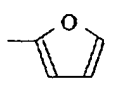

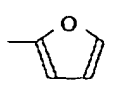

表-1 (つづき)

3 1		$\begin{array}{c} \text{---CH---} \text{C}_6\text{H}_5 \\ \\ \text{C}_2\text{H}_5 \end{array}$	
3 2		$\begin{array}{c} \text{---CH---} \text{C}_6\text{H}_{11} \\ \\ \text{CH}_3 \end{array}$	
3 3		$\begin{array}{c} \text{---} \text{C}_6\text{H}_4 \text{---} \text{CH}_3 \\ \\ \text{H} \end{array}$	
3 4		$\begin{array}{c} \text{---} \text{C}_6\text{H}_4 \text{---} \text{CH}_3 \\ \\ \text{H} \end{array}$	
3 5		$\begin{array}{c} \text{---CH---C}_2\text{H}_5 \\ \\ \text{CH}_3 \end{array}$	
3 6		$\begin{array}{c} \text{---CH---C}_3\text{H}_7^a \\ \\ \text{CH}_3 \end{array}$	
3 7		$\begin{array}{c} \text{---CH---C}_3\text{H}_7^i \\ \\ \text{CH}_3 \end{array}$	
3 8		$\begin{array}{c} \text{---CH---CH}_2\text{CH}(\text{CH}_3)_2 \\ \\ \text{CH}_3 \end{array}$	

【0023】

【表6】

表-1 (つづき)

39		$\begin{array}{c} -\text{CH}-\text{C}_2\text{H}_5 \\ \\ \text{C}_2\text{H}_5 \end{array}$	
40		$-\text{CH}_2\text{C}_4\text{H}_9^t$	
41		$\begin{array}{c} -\text{CH}-\text{C}_6\text{H}_5 \\ \\ \text{CH}_3 \end{array}$	
42		$\begin{array}{c} -\text{CH}-\text{C}_6\text{H}_{11} \\ \\ \text{CH}_3 \end{array}$	
43		$\begin{array}{c} -\text{CH}-\text{C}_6\text{H}_5 \\ \\ \text{CH}_3 \end{array}$	
44		$\begin{array}{c} -\text{CH}-\text{C}_6\text{H}_5 \\ \\ \text{C}_2\text{H}_5 \end{array}$	
45		$\begin{array}{c} -\text{CH}-\text{C}_6\text{H}_{11} \\ \\ \text{CH}_3 \end{array}$	
46		$\begin{array}{c} -\text{CH}-\text{C}_6\text{H}_5 \\ \\ \text{CH}_3 \end{array}$	
47		$\begin{array}{c} -\text{CH}-\text{C}_6\text{H}_{11} \\ \\ \text{CH}_3 \end{array}$	

【0024】かかるアミノピリダジン誘導体は、欧州公開特許公報第449203号または同第534443号に記載の化合物であり、いずれの化合物も同公報に記載の方法に従って合成できる。本発明の平滑筋細胞増殖に起因する疾患の治療・予防剤は、血管内腔で生じる平滑筋細胞の遊走、増殖に起因する各種疾患に対して効果を有する。具体的には、PTCA術後の再狭窄、経皮的動脈拡張術(PTA)後の再狭窄、心臓、肝臓、腎臓、血管等の臓器移植後等における血管狭窄の予防もしくは治療に使用される。

【0025】本発明のアミノピリダジン誘導体を平滑筋細胞増殖に起因する疾患の治療・予防剤として臨床に応用するに際し、経口的に用いる場合は、成人に対し1回1~200mgを1日1~3回投与するのが好ましく、静脈注射の場合は、成人に対し1回0.01~10mgを1日1~5回投与するか1日0.01~50mgを持続注入するのが好ましく、また、直腸内投与の場合は、1回1~100mgを1日1~3回投与するのが好ましい。また、以上の投与量は、年齢、病態、症状により適宜増減することが更に好ましい。

【0026】製剤化に際しては、アミノピリダジン誘導

30 体あるいはその薬学的に許容される塩の1種または2種以上を、通常用いられる製薬用担体、賦形剤その他の添加物と混合する。担体は固体でも液体でもよく、固体担体の例としては乳糖、白陶土(カオリン)、ショ糖、結晶セルロース、コーンスターチ、タルク、寒天、ペクチン、アカシア、ステアリン酸、ステアリン酸マグネシウム、レシチン、塩化ナトリウムなどが挙げられる。

【0027】液状の担体の例としては、シロップ、グリセリン、落花生油、ポリビニルピロリドン、オリーブ油、エタノール、ベンジルアルコール、プロピレングリコール、水などが挙げられる。医薬製剤は、種々の剤形をとることができ、固体担体を用いる場合は、錠剤、散剤、顆粒剤、硬ゼラチンカプセル剤、坐剤またはローチ剤とすることができる。固体担体の量は広範に変えることができるが、好ましくは約1mg~約1gとする。液状の担体を用いる場合は、シロップ、乳液、軟ゼラチンカプセル、更にアンプル入りのような滅菌注射液または水性もしくは非水性の懸濁液とすることができる。

【0028】

【実施例】以下、実施例により本発明をさらに具体的に説明するが、本発明はその要旨を越えない限り以下の実

施例により限定されるものではない。

【0029】合成例

(R)-1-(1-シクロヘキシルエチルアミノ)-4-フェニルフタラジン〔前記表-1における化合物No. 17の(R)体〕のフマル酸塩(以下、「化合物A」と略記する)の合成。

N-メチルピロリドン400mlに1-クロロ-4-フェニルフタラジン144.4g(0.6mol)、

(R)-(-)-1-シクロヘキシルエチルアミン230g(1.8mol)を添加した後、混合物を120～130℃にて6時間加熱攪拌した。反応終了後、冷却し、5%NaOH水溶液4.0lを添加し、クロロホルムにて抽出した。有機層をMgSO₄にて乾燥後、濃縮し、シリカゲルカラムクロマトグラフィー(溶離液、酢酸エチル:ヘキサン:クロロホルム=1:3:1)にて精製し、エーテル-クロロホルムより再結晶を行い、

(R)-1-(1-シクロヘキシルエチルアミノ)-4-フェニルフタラジン150.2gを合成した。融点164.0～167.0℃

【0030】こうして得られた(R)-1-(1-シクロヘキシルエチルアミノ)-4-フェニルフタラジン100.0g、フマル酸32.0gをメタノール1.0lに加え16時間還流下攪拌した。攪拌しながら20℃まで自然に冷却させ、結晶をろ取し、メタノール200mlで洗浄し、約60℃1～2mmHgで乾燥し、フマル酸121.5gを得た。融点240～250℃(分解)

【0031】実施例1

ラット内膜肥厚モデルに対する作用

ペントバルビタール麻酔下SDラット(20週令)を背位固定し、左頸動脈を露出した。外頸動脈より、血栓除去用フォガティ-カテーテル(2フレンチ)をバルーンを膨らませない状態で、大動脈分岐部まで挿入した(約5cm)。バルーンを膨らませ、回転させながら挿入部まで引いた。この操作を3回繰り返して、頸動脈の内皮細胞を剥離した。操作終了後、カテーテルを引き抜き、外頸動脈を結索し、医療用クリップで切開部を閉じ合わせた。化合物Aは、0.7%トラガント溶液に懸濁し、1mg/kg、3mg/kgまたは10mg/kgの用量で1日1回、経口投与した。対照群には、0.7%トラガント溶液を同様に経口投与した。1日目の投与は、頸動脈内膜剥離直後に行なった。

【0032】内膜剥離から2週間後、ペントバルビタール麻酔下、3%エバンスブルーを大腿静脈より静脈内投与した。30分後開腹し、0.01Mリン酸緩衝液で大動脈より全身灌流した後、頸動脈を摘出した。摘出した頸動脈の内皮細胞剥離が確認された部分を、6～8個の長さ2mmの動脈片にしてホルマリン固定してから、パラフィン包埋した。各ブロックより横断面の組織切片を作製し、エラスチカ・ワンギーソン染色を行った。各切片の内膜・中膜の面積をデジタイザーで測定し、内膜肥厚度は内膜/中膜の面積比で表した。結果を表-2に示す。化合物Aは、内膜剥離によるラット頸動脈内膜肥厚を用量依存的に抑制した。

【0033】

【表7】

表-2

	用 量	例数	内膜/中膜の面積比±標準誤差
対 照		14	1.060±0.081
化合物A	1mg/kg	7	0.853±0.107
	3mg/kg	8	0.637±0.067*
	10mg/kg	9	0.462±0.094*

*: p<0.05 (検定法) 一元配置分散分析 Dunnett 型

【0034】実施例2

ラット内膜肥厚モデルに対する作用

ペントバルビタール麻酔下SDラット(20週令)を背位固定し、左頸動脈を露出した。外頸動脈より、血栓除去用フォガティ-カテーテル(2フレンチ)をバルーンを膨らませない状態で、大動脈分岐部まで挿入した(約5cm)。バルーンを膨らませ、回転させながら挿入部まで引いた。この操作を3回繰り返して、頸動脈の内皮細胞を剥離した。操作終了後、カテーテルを引き抜き、

外頸動脈を結索し、医療用クリップで切開部を閉じ合わせた。化合物Aは、0.7%トラガント溶液に懸濁し、3mg/kgの用量で1日1回、経口投与し、対照群には0.7%トラガント溶液を同様に経口投与した。A群では1回目の投与は、頸動脈内膜剥離直後に行ない、B群では頸動脈内膜剥離4日後より開始した。内膜剥離から2週間後、ペントバルビタール麻酔下、3%エバンスブルーを大腿静脈より静脈内投与した。30分後開腹し、0.01Mリン酸緩衝液で大動脈より全身灌流した

後、頸動脈を摘出した。

【0035】摘出した頸動脈の内皮細胞剥離が確認された部分を、6～8個の長さ2mmの動脈片にして、ホルマリン固定してから、パラフィン包埋した。各ブロックより横断面の組織切片を作製し、エラスチカ・ワンギンソン染色を行った。各切片の内膜・中膜の面積をデジタルイザースで測定し、内膜肥厚度は内膜／中膜の面積比で表

した。その結果を表-3に示す。化合物Aは3mg/kgの経口投与で、内膜剥離によるラット頸動脈内膜肥厚を抑制し、頸動脈内膜剥離4日後からの投与でも有意であった。

【0036】

【表8】

表-3

	投与期間 (日)	例数	内膜／中膜の面積比±標準誤差
対 照		7	1.033±0.086
化合物A	A 0～14	6	0.568±0.037*
	B 4～14	6	0.594±0.044*

* ; p < 0.05 (検定法) 一元配置分散分析 Dunnett 型

【0037】

【発明の効果】アミノピリダジン誘導体は、平滑筋細胞の遊走、増殖を抑制するので、平滑筋細胞増殖に起因する疾患、例えば経皮的冠動脈拡張術(PTCA)後の再

20 狭窄、心臓、肝臓、腎臓、血管等の臓器移植後の血管狭窄、経皮的動脈拡張術(PTA)後の再狭窄の予防もしくは治療に有用である。

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